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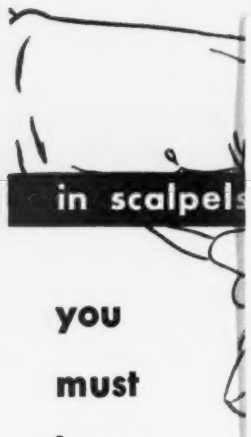

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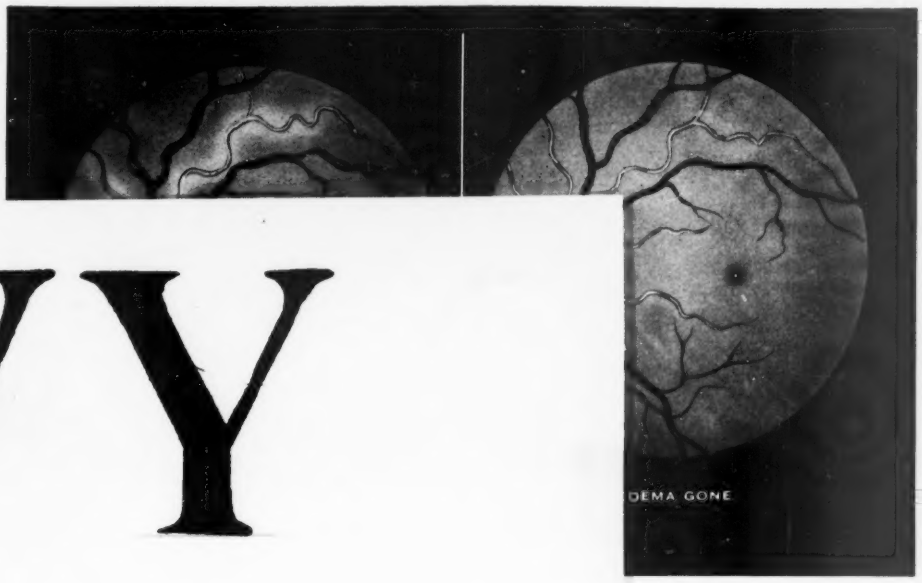

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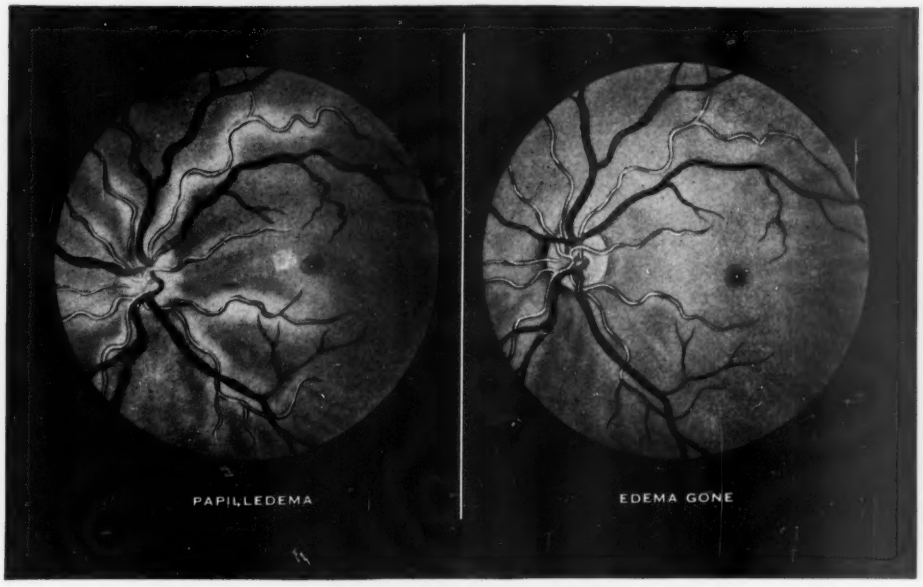

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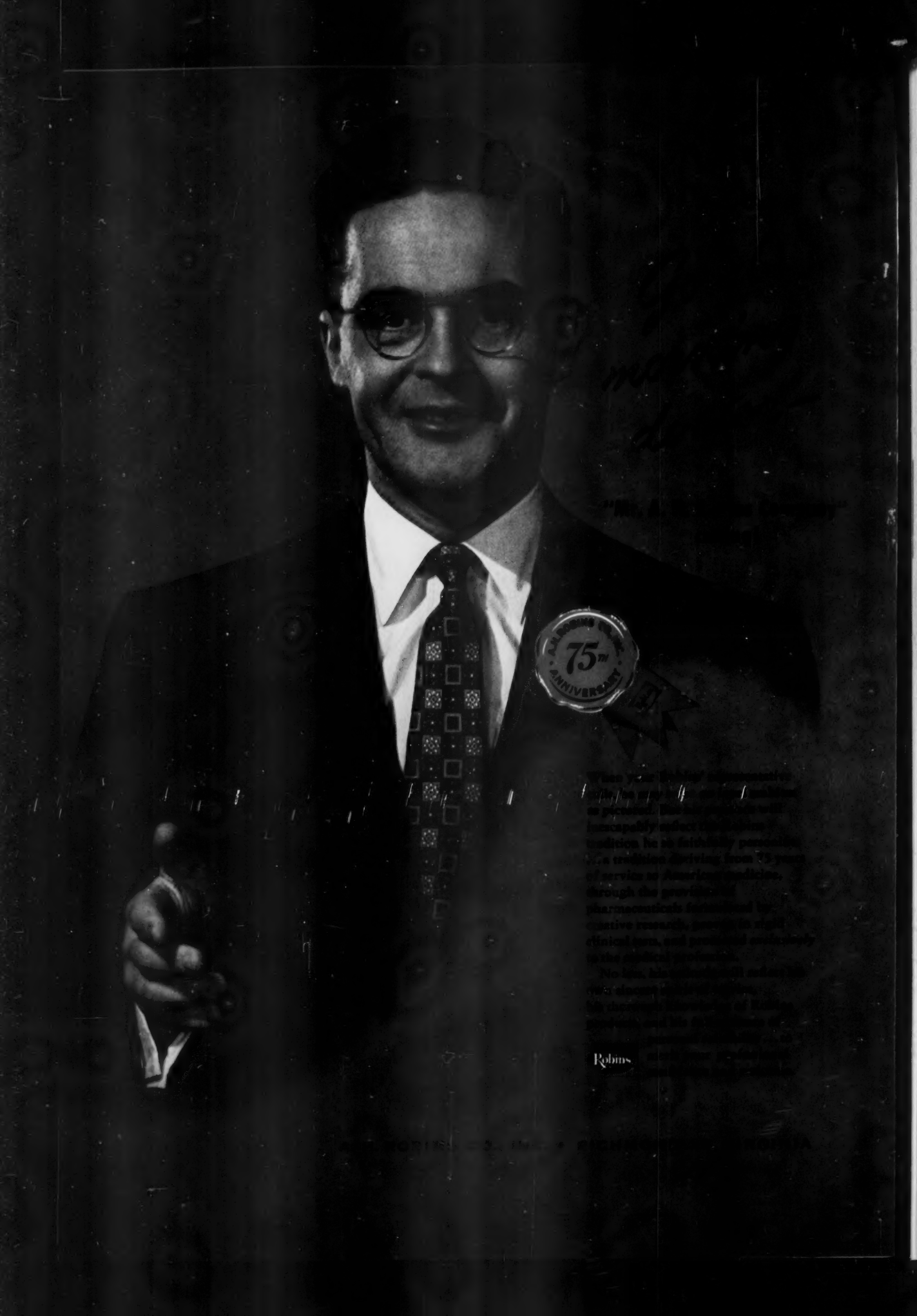
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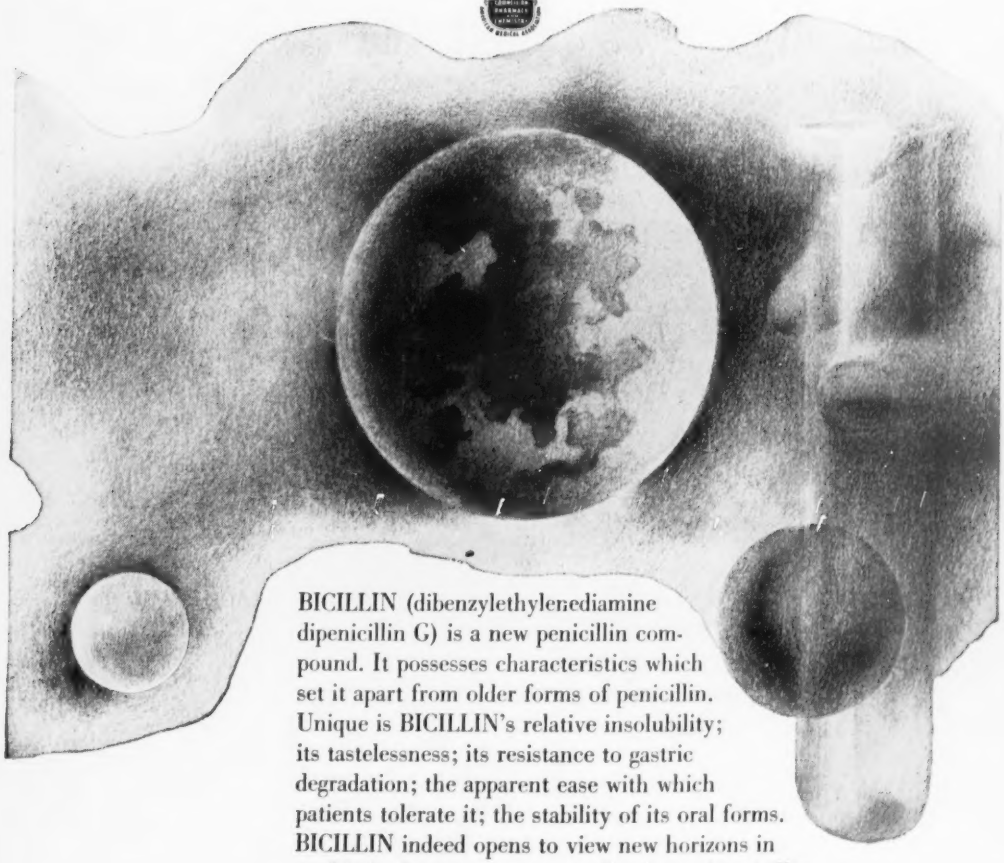

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1. Van Alyea, O. E., and Donnelly, Allen: *Arch. Otolaryng.*, 49:234, Feb., 1949.

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Volume 249 JULY 2, 1953 Number 1

THE EFFECT OF PENICILLIN PROPHYLAXIS ON STREPTOCOCCAL DISEASE RATES AND THE CARRIER STATE*

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CAPTAIN GEORGE C. ECKHARDT, MC, USAR,‡ MAJOR HAROLD B. HOUSER, MC, USAR,‡
AND MAJOR EDWARD O. HAHN, MC, USAR‡

CRITICAL situations arise in the armed forces during periods of mobilization when the incidence of streptococcal pharyngitis and tonsillitis reaches such levels as to interfere seriously with military training and operations. Complete information about the most feasible method for preventing or terminating these epidemics is lacking. This report presents the findings of several field trials conducted at an Air Force base for the purpose of evaluating penicillin as an agent for prophylaxis of epidemic streptococcal disease. The observations are divided into two parts: pilot studies comparing the effects of several regimens of penicillin on the carrier state in small selected groups of men, all of whom were harboring Group A streptococci; and a large-scale field program evaluating the effects of oral penicillin prophylaxis on streptococcal carrier and disease rates.

STUDIES AND METHODS

The men included in these studies were stationed at Francis E. Warren Air Force Base, Wyoming, a technical training center where airmen are sent for periods of eight to thirty weeks for instruction in various ground occupations. Streptococcal pharyngitis has been prevalent for a number of years at this military installation.[1, 2] The pilot studies reported here were done between November 22, 1950, and February 23, 1951, and between January 4 and March 26, 1952. The observations of the large-scale study were made between March 19 and May 13, 1951. During the winter of 1951, Type 14 was the prevalent streptococcus at this installation, whereas in 1952 Types 1, 3, 6, 18 and 30 also became common.

Table 1 presents the various preparations, dosages and routes of administration of penicillin,

TABLE 1. *Distribution of Men in the Various Studies According to Preparation and Dosage of Penicillin.*

PREPARATION	ROUTE OF ADMINISTRATION	DOSAGE	NO. OF MEN	
			DRUG	PLACEBO OR CONTROL*
Pilot study:				
Crystalline penicillin G buffered with calcium carbonate	Oral	1,000,000 units twice daily for 5 days	10	11[a]
		1,000,000 units twice daily for 10 days	29	28[b]
		500,000 units twice daily for 10 days	14	15[c]
		250,000 units once daily for 10 days	20	10
Procaine penicillin G, with 2% aluminum monostearate in peanut oil	Intramuscular	Single injection of 600,000 units	11	11[a]
		Four injections of 600,000 units each, one every other day	29	28[b]
Benzethacil (dibenzylethylenediamine penicillin G)	Intramuscular	Two simultaneous injections, each containing 900,000 units	10	12[d]
		Single injection of 600,000 units	27	27[c, d]
Large-scale study:				
Crystalline penicillin G buffered with calcium carbonate	Oral	1,000,000 units twice daily for 10 days	1372	2254
		1,000,000 units twice daily for 5 days	1310	

*Similar superscripts (a, b, c, etc.) indicate common control groups.

Table 1 presents the various preparations, dosages and routes of administration of penicillin,

*From the Streptococcal Disease Laboratory, Francis E. Warren Air Force Base, Wyoming, and the Department of Preventive Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.

This investigation was conducted under the sponsorship of the Commission on Acute Respiratory Diseases and the Commission on Streptococcal Diseases, Armed Forces Epidemiological Board, and was supported by the Offices of The Surgeons General, Departments of the Army and Air Force, Washington, D. C.

†Formerly, research associate in preventive medicine, Western Reserve University School of Medicine.

‡Formerly, fellow in preventive medicine, Western Reserve University School of Medicine.

§Professor of medicine and associate professor of preventive medicine, Western Reserve University School of Medicine.

as well as the number of men in the control and treated groups for both the pilot and large-scale studies. Penicillin was administered orally either two hours after or fifteen to thirty minutes before meals. When the antibiotic was given orally twice a day, the two dosages were separated by an interval of nine to twelve hours. In the pilot studies, injections of physiologic saline solution or capsules containing lactose were administered as placebos. No placebos were given in the large-scale study.

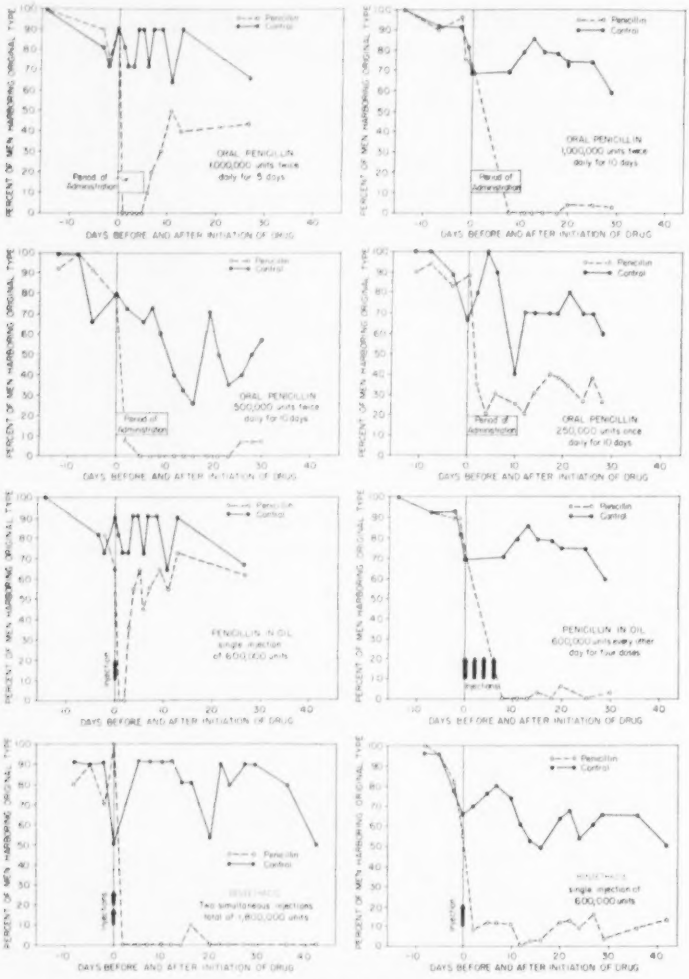
PERCENT OF MEN HARBORING ORIGINAL TYPE
DAYS BEFORE AND AFTER INITIATION OF DRUG
Penicillin
Control
ORAL PENICILLIN
1,000,000 units twice daily for 5 days
Period of Administration
ORAL PENICILLIN
1,000,000 units twice daily for 10 days
ORAL PENICILLIN
500,000 units twice daily for 10 days
ORAL PENICILLIN
250,000 units once daily for 10 days
PENICILLIN IN OIL
single injection of 600,000 units
PENICILLIN IN OIL
600,000 units every other day for four doses
Injection
Injections
Two simultaneous injections total of 1,800,000 units
Single injection of 600,000 units

FIGURE 1. *Pilot Studies on the Effect of Penicillin on the Carrier State of Group A Streptococci.*

Cultures from the nose and throat were taken with dry sterile cotton swabs. Two methods were employed for the isolation of beta-hemolytic streptococci. The swab was either incubated in Pike's selective broth[3] for eighteen hours and then subcultured on sheep-blood agar or streaked directly onto sheep-blood agar. Stabs were made into the blood-agar plates to determine the type of subsurface hemolysis.[4] Streptococci exhibiting beta hemolysis on the surface or in the stab were selected for classification according to the methods of Maxted[5] and Swift, Wilson and Lancefield.[6] All cultures taken during the periods of penicillin administration were obtained in the morning before the first penicillin dose for that day.

For the pilot studies, men harboring Group A streptococci were chosen on the basis of the results of three or four cultures of the throat and nose taken over a period of five to ten days. Only those from whom Group A streptococci were recovered on at least two occasions by the direct-streak technic were included. After selection of suitable

"carriers" for inclusion in these studies, the technic by which each succeeding culture was examined was determined by the findings of the preceding culture: if ten or fewer colonies of beta-hemolytic streptococci were present on the preceding culture, both the direct-streak and the more sensitive Pike technic were employed; if no beta-hemolytic streptococci were found, only the Pike technic was used. Nose cultures were obtained routinely from only men in whom Group A streptococci had been isolated from the nose during the initial period of selection. The intervals at which cultures were taken are indicated in Figure 1. The men in the pilot studies were scattered among several squadrons, and no effort was made to isolate them during the four to six weeks of observation.

In the large-scale prophylaxis study, no attempt was made to include only men harboring Group A streptococci. Entire squadrons of approximately 400 men each were given penicillin by mouth. Squadrons were selected for the treated and control groups on the basis of comparable programs of training, strengths and previous hospital rates for streptococcal disease. Three squadrons received penicillin for five and 3 for ten days, and 4 were given no medication (Table 1).

The personnel of a squadron were housed and fed as a unit, but there was mingling among squadrons during classes and other activities. In addition, squadrons were continually receiving and losing men. During the large-scale prophylaxis study, the average weekly rate of turnover for the control group was 14 per cent in and 13 per cent out. For the group receiving penicillin for ten days it was 12 per cent in and 13 per cent out; for the group receiving the drug for five days it was 6 per cent in and 8 per cent out. Usually these were inter-base transfers, but there were some intra-base transfers, particularly among men returning from the hospital. Thus, the squadrons were constantly subject to introductions from the outside of personnel harboring streptococci, a normal situation that exists in many military units.

During the eleven-week period of observation in the large-scale study all personnel admitted to the hospital because of respiratory disease were examined for the presence of exudate on the pharynx or tonsils and cultured by the direct-streak technic for beta-hemolytic streptococci in the throat. In the squadrons receiving penicillin, personnel were instructed to report to sick call upon the appearance of skin rashes, and the incidence of these and other reactions was recorded. Samples of the treated and control groups were also questioned for the occurrence of gastrointestinal complaints.

Pilot Studies on Eradication of the Carrier State

As pilot studies to determine the effect on the carrier state, various preparations and dosages of penicillin were given to small groups of men harboring Group A streptococci. Penicillin was administered orally as crystalline penicillin G and intramuscularly as procaine penicillin in oil with 2 per cent aluminum monostearate or as benzethacil.* Details of the preparations, dosages and routes of administration, as well as the number of carriers in the various treated and control groups, are given in Table 1. Figure 1 represents graphically the percentage of men in the various treated and control groups who continued to harbor Group A streptococci of the same type in the throat at various intervals before and after initiation of drug or placebo.

As shown in Figure 1, control groups of "carriers" cultured at the same time drug evaluations were being performed showed in general a gradual and moderate decline in the percentage of men from whom streptococci of the same type were isolated. With one exception, about 60 per cent of the men in the various control groups continued to harbor the same type of organism at the termination of observations. In the study on the effect of 500,000 units of penicillin given by mouth twice daily, the control group showed a more rapid but erratic disappearance of the carrier state.

When given by mouth for five days, 1,000,000 units of penicillin twice daily failed to eradicate the carrier state in about 45 per cent of the carriers studied, although no Group A streptococci were isolated from the throat during the period of daily administration. This same dosage for ten days was almost always effective in eliminating the carrier state. Half this dosage administered twice daily for ten days also seemed to be effective, although it is difficult to interpret the results in this group because of the relatively large percentage of the control group that cleared spontaneously. When the dosage was reduced to 250,000 units once daily for ten days, the same type of organism persisted in a fourth of the men during oral administration of penicillin and was cultured from a third of the group after the antibiotic was discontinued.

When a single injection of 600,000 units of procaine penicillin in oil was given to carriers, no beta-hemolytic streptococci were isolated from the throat for two days, but on the third day the original type of streptococcus was recovered from a third of the group and the percentage of men harboring the same type soon approached that of the control group. Four such injections administered every other day resulted in eradication of the organism in almost every case.

Elimination of the carrier state was observed in all of 10 men who received 1,800,000 units of benzethacil in two simultaneous injections. A single injection of 600,000 units seemed equally effective in 90 per cent of the carriers studied. No manifestations of toxicity or hypersensitivity were ob-

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served after benzethacil, but the men frequently volunteered the information that this injection caused more local discomfort than previous injections of penicillin that they had received.

When the same type of streptococcus was isolated before and after administration of penicillin, the penicillin resistance of the two strains was tested. All strains were sensitive to 0.05 units or less of penicillin, and no increased resistance was found in the strains isolated after exhibition of the drug.

Since only a small proportion (about 30 per cent) of the carriers in the pilot studies was shown to harbor Group A streptococci in both the nose and throat, it was difficult to assess the effect of penicillin in such persons. As shown in Table 2 the results in nasal carriers roughly paralleled those of the total group. However, the failures observed, especially those from the more successful regimens, were frequently in nasal carriers.

Table 2 also shows the number of men from the various pilot-study groups who acquired new types of streptococci. New types were isolated in 0 to 25 per cent but were rarely found during the period of drug administration. In the two groups who received benzethacil occasional acquisitions occurred during the first three days after the injections, but the majority of new types did not appear until at least two weeks after the injections.

TABLE 2. *Effect of Various Penicillin Regimens on the Eradication of Streptococci from Nasal Carriers and on the Acquisition of New Types of Streptococci.*

ROUTE	PREPARATION	DOSAGE	ERADICATION OF STREPTOCOCCI FROM NASAL CARRIERS		ACQUISITION OF NEW TYPES	
			NO. OF NASAL CARRIERS	NO. FROM WHOM STREPTOCOCCI WERE ERADICATED	TOTAL NO. OF CARRIERS	NO. ACQUIRING NEW TYPES
Oral	Crystalline penicillin	1,000,000 units twice daily for 5 days	3	1	10	1
		1,000,000 units twice daily for 10 days	6	5	29	3
		500,000 units twice daily for 10 days	7	6	14	3
		250,000 units once daily for 10 days	9	2	20	5
Intramuscular	Procaine penicillin in oil	Single injection of 600,000 units	3	1	11	0
		Four injections of 600,000 units, each one every other day	7	7	29	1
Intramuscular	Benzethacil	Two simultaneous injections of 900,000 units each	4	4*	10	1
		Single injection of 600,000 units	10	7	27	3
—	Placebo (total control group)	Varying regimens (physiologic saline solution or lactose capsules)	33	2	76	8

*Three of these continued to show the same type of streptococcus sporadically in the nose culture by the Pike technic.

Large-Scale Prophylaxis Study

In the large-scale study 1,000,000 units of penicillin was administered orally twice daily for either five or ten days to entire squadrons of men. The effects of this drug on the carrier rates, the incidence of disease and the occurrence of reactions were recorded.

To estimate the effect of penicillin on the carrier rates in the three groups, we examined approximately 150 men from each group by streaking throat swabs directly onto sheep-blood agar and reading for the presence of beta-hemolytic streptococci.* Figure 2 shows the results of these surveys. The carrier rate for the control group remained relatively constant throughout the period of observation although the initial survey showed a lower rate than that of the other two groups. Three days after penicillin had been discontinued the carrier rates had markedly diminished in both the treated groups. Fifteen days after the last dose of penicillin the rate in the group receiving the drug for five days was only slightly less than that of the control group whereas the carrier rate in the group receiving penicillin for ten days was approximately

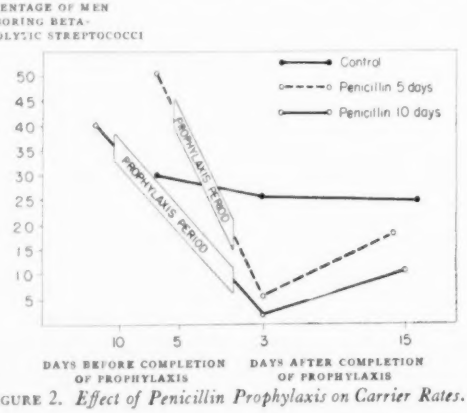

FIGURE 2. *Effect of Penicillin Prophylaxis on Carrier Rates.*

*In contrast to the procedure in the pilot studies, the same groups of men were not followed throughout, and beta-hemolytic streptococci were not classified so that it is impossible to determine if the same or new types of streptococci were being isolated.

half that of the control group. These rates include only men who received the entire dose of drug, or those in the control group who were present during the period of administration. Inclusion of men who missed part of the dosage or who moved into the squadron after administration of the drug would result in slightly higher rates for the groups receiving prophylaxis.

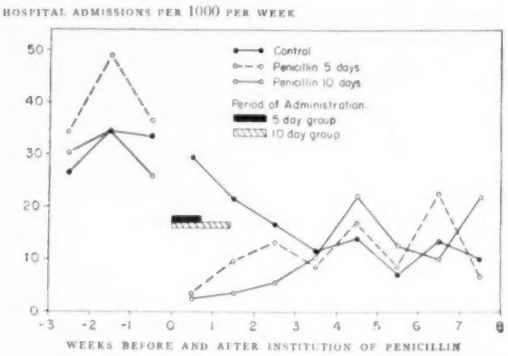

FIGURE 3. *Effect of Penicillin Prophylaxis on Streptococcal Disease Rates of Squadrons in the Large-Scale Study.*

Figure 3 shows the effect of penicillin prophylaxis on the over-all incidence of hospital admissions for streptococcal disease among entire squadrons, and Table 3 gives the basic data from which this figure is derived. For the purposes of this analysis, all men admitted to the hospital with respiratory disease who had exudative pharyngitis or tonsillitis or both, or from whom beta-hemolytic streptococci were isolated, were considered to have streptococcal infection. The criteria for admission to the hospital included all men with exudative lesions of the throat and all men with a temperature of 100°F. or greater. Streptococcal disease rates for the three groups showed some variation during the two weeks before the institution of prophylaxis. During the period of administration of penicillin there was a sharp fall in the rate in the groups receiving the drug. These rates began to rise again rather soon after the cessation of drug prophylaxis, and after three weeks the incidence of hospital admissions for streptococcal infections was approximately equal for the three groups. The rates in the groups receiving penicillin never regained their original levels, but there was also a gradual decline in the disease rate for the control group. It is interesting that the curve for disease rates for the control group can almost be superimposed on that for the entire base during this period.

TABLE 3. *Incidence of Streptococcal Disease among Squadrons before and after Large-Scale Penicillin Prophylaxis.*

Weekly Period	Average Total Strength			Hospital Admissions for Streptococcal Infection			Disease Rate (Admissions/1000/Week)		
	Penicillin for 10 days	Penicillin for 5 days	Control group	Penicillin for 10 days	Penicillin for 5 days	Control group	Penicillin for 10 days	Penicillin for 5 days	Control group
Feb. 26–Mar. 4	1195	929	1971	36	32	54	30.1	34.4	27.4
Mar. 5–11	1241	1257	1856	43	62	64	34.6	49.3	34.5
Mar. 12–18	1234	1212	2078	32	45	70	25.9	37.1	33.7
Mar. 19*–25	1372	1310	2254	4	5	66	2.9	3.8	29.3
Mar. 26–Apr. 1	1379	1370	2355	5	13	51	3.6	9.5	21.7
Apr. 2–8	1305	1427	2344	7	19	40	5.4	13.3	17.1
Apr. 9–15	1215	1388	2152	13	15	24	10.7	10.8	11.2
Apr. 16–22	1122	1297	1816	25	22	26	22.3	17.0	14.3
Apr. 23–29	1031	1206	1912	13	10	14	12.6	8.3	7.3
Apr. 30–May 6	993	1112	2024	10	25	26	10.0	22.5	12.8
May 7–13	1045	1032	1976	23	8	17	22.0	7.8	8.6

*Date prophylaxis was initiated.

Disease rates including only men remaining in the squadron who had received at least three fourths of their drug are shown in Table 4.* This table demonstrates that the number of such persons in the

TABLE 4. *Incidence of Streptococcal Disease among Men in the Large-Scale Study Who Were Present during the Time of Drug Administration.*

Weekly Period	Average No. of Men Remaining Who Received Prophylaxis			Hospital Admissions for Streptococcal Infection			Disease Rate (Admissions/1000/Week)		
	Penicillin for 10 days	Penicillin for 5 days	Control group	Penicillin for 10 days	Penicillin for 5 days	Control group	Penicillin for 10 days	Penicillin for 5 days	Control group
Mar. 19*–25	1372	1310	2254	4	5	66	2.9	3.8	29.3
Mar. 26–Apr. 1	1295	1204	1907	5	10	41	3.9	8.3	21.5
Apr. 2–8	1209	1150	1731	4	12	31	3.3	10.4	17.9
Apr. 9–15	1116	1118	1412	7	10	18	6.3	8.9	12.7
Apr. 16–22	938	963	922	16	17	18	17.0	17.7	19.5
Apr. 23–29	786	871	710	8	6	6	10.2	6.9	8.5
Apr. 30–May 6	584	735	583	5	19	12	8.6	25.9	20.6
May 7–13	486	597	343	11	3	6	22.6	5.0	17.5

*Date prophylaxis was initiated.

*During the time of drug administration, obviously, not everyone had received three fourths of his medication at the time he became ill. For the sake of simplicity the entire population unit was considered as treated during this period.

population steadily decreased as a result of turnover but that the rates were approximately the same as the unadjusted rates of the entire units.

The incidence of penicillin reactions was low. Moderate laryngeal edema developed in 1 man. In the group receiving penicillin for ten days, 14 men (1 per cent) manifested definite skin reactions and another 11 men had questionable skin reactions. Three men (0.2 per cent) from the group receiving drug for five days showed definite skin sensitivity, and 6 men had questionable skin reactions. A sample (169 men) from the group receiving prophylaxis for ten days was questioned regarding symptoms of diarrhea. Sixty per cent reported loose stools during the time the drug was being administered, and 10 per cent observed loose stools after the drug had been discontinued. No loose stools were reported by 37 men from the control group who were similarly questioned.

Discussion

Extensive programs of sulfadiazine prophylaxis instituted in military units during World War II were initially successful in controlling epidemics of streptococcal infection,[7, 8] but there were a few fatal reactions to the drug and the emergence of sulfonamide-resistant strains resulted in the eventual return of high disease rates.[9, 10] No such large-scale programs have been reported with penicillin although theoretically this drug has several advantages over the sulfonamides. Penicillin resistance has never been observed among freshly isolated strains of Group A streptococci,[11] and the incidence of serious drug reactions may be less with penicillin than with the sulfonamides. In addition, with penicillin it is possible to eradicate Group A streptococci from the oropharynx, whereas sulfonamides merely suppress streptococcal growth.[12, 13]

Although suppression of streptococcal growth or interference with new acquisitions may be all that is necessary to check an epidemic in a military installation, such prophylaxis would probably not prevent spread to other installations not receiving prophylaxis.[14] Furthermore, continuous administration of the suppressive drug for long periods would probably be necessary.[7] Such long-term programs are difficult to enforce. Short-term, intermittent administration of a bactericidal agent would be more feasible in most military situations. The pilot studies reported here demonstrate that penicillin will eradicate Group A streptococci from carriers if it is given over a sufficiently long period and in large enough doses.

These studies indicate that it is probably necessary for penicillin to be given for approximately ten days to eliminate Group A streptococci from the throats of carriers. They confirm the report of Rantz, Spink and Boisvert,[15] who found that short courses of penicillin were ineffective, and the work of Goerner, Massell and Jones,[16] who were usually able to eradicate the carrier state after ten days of penicillin. These findings on the chronic carrier state contrast with the observations in acute streptococcal infections, in which one injection of procaine penicillin in oil containing 2 per cent aluminum monostearate will frequently eliminate the carrier state although this is not recommended as optimal therapy.[17] In experimental infections of animals Eagle[18] also related the age of the infection to the curative dose of penicillin.

From the pilot studies reported here a dosage of 500,000 to 1,000,000 units orally twice daily seems adequate to eliminate the carrier state if the drug is administered for ten days. Although 250,000 units once daily proved ineffective in the studies reported here, Massell, Dow and Jones[19] obtained fairly good results with 100,000 units three times a day. Perhaps 250,000 units twice daily would also prove successful.

Effective intramuscular regimens include 600,000 units of procaine penicillin in oil with 2 per cent aluminum monostearate every other day for four doses and a total of 1,800,000 units of benzethacil divided into two simultaneous injections. For large groups the administration of daily oral medication is more practical than multiple injections. A single injection or two simultaneous injections of benzethacil might be feasible even in large groups. This preparation warrants further investigation; 1,000,000 units in a single injection might prove to be an adequate dosage. In the present study new types of streptococci were isolated about two weeks after the injections of benzethacil, indicating that the concentration of penicillin in these men was very low at this interval. This contrasts with observations in children indicating that measurable amounts of penicillin persist in the body for three weeks after a single injection of 1,250,000 units of benzethacil.[20]

The results of the large-scale prophylaxis studies indicate that it is possible to reduce the incidence of streptococcal disease by oral administration of penicillin. The differences between the men receiving the drug and the control group were striking during the period of administration, but a few weeks after the drug had been discontinued, the rates in the treated groups returned to levels comparable to those of the control group. The effect was of somewhat longer duration in the group receiving ten days of drug than in the group receiving only five days. It is impossible to conjecture whether or not the disease rates would have returned to the original high levels after the cessation of penicillin if the epidemic had not been waning. The results would have been more impressive, of course, if the rates in the control group had remained constant. From the data obtained it seems likely that short-term penicillin prophylaxis, when given under conditions similar to those in this study, may have to be repeated every three or four weeks

until the epidemic declines. In other military units or situations it may not be necessary to repeat prophylaxis at such relatively frequent intervals. When the results of this study are interpreted, it must be emphasized that the treated units were neither static nor isolated population groups. The reduction in disease rates might have been more lasting if the turnover had been less or if the entire installation had been treated so that contacts with untreated groups would have been eliminated. In any given situation the frequency with which such a program should be reinstituted can be gauged by carrier surveys or disease rates.

In the large groups receiving penicillin by mouth, the incidence of reactions was low (approximately 1 per cent) except for minimal or moderate diarrhea. The only serious reaction was moderate laryngeal edema, which developed in 1 man. It appears that penicillin is a relatively safe drug for large-scale prophylaxis.

Although strains of streptococci were not tested for penicillin resistance during the large-scale prophylaxis program, no evidence was obtained that a resistant strain became predominant in the population. This does not preclude the possibility that an unrecognized resistant strain did appear or that resistant strains would emerge and become predominant if penicillin were administered continuously for a long period.

These studies suggest that short-term intermittent administration of a bactericidal drug such as penicillin may be an effective method for the prophylaxis of streptococcal disease and may have certain advantages over the continuous exhibition of suppressive agents such as the sulfonamides. During times of emergency large quantities of penicillin may not be readily available, in which case sulfadiazine may be employed for prophylaxis and penicillin used for treatment of streptococcal infections. Such a regimen should be successful until sulfonamide-resistant strains become prevalent in the population.

Conclusions

Oral administration of penicillin eradicated Group A streptococci from the throats of carriers when given in a dosage of 1,000,000 units twice daily for ten days and was probably effective in half this dosage. A dosage of 250,000 units once daily for ten days did not suppress or eradicate the carrier state in many men harboring these organisms. A single intramuscular injection of 600,000 units of procaine penicillin in oil failed to eradicate Group A streptococci, but four similar injections administered every other day were effective in almost every case. Benzethacil given as a single injection of 600,000 units or two simultaneous injections totaling 1,800,000 units successfully eradicated the carrier state.

The streptococcal disease rates and carrier rates were reduced for two or three weeks in large groups of men who received 1,000,000 units of penicillin by mouth twice daily for five or ten days.

We are indebted to Colonel Charles Backes, post commander, and Colonel Howard F. Currie and Colonel Larry A. Smith for their co-operation, as well as to the many squadron commanders and noncommissioned officers who co-operated actively in the administration of the drugs. The assistance of the following members of the laboratory staff is acknowledged: Captain Chandler A. Stetson, Lieutenant Earl C. Marple, Elmer Kohlmiller, Richard M. Krause, Kenzo Kuroda, S/Sgt. Frederick Barkmann, Mary K. Carter, Lorraine Hayman, Emily Lambert, Phyllis McGlathery, Katherine Mosley, Terry Schreiber, Martha Smiddle, T/Sgt. William H. Stroud and Ernestine Vollman.

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INTRACARDIAC PUNCTURE IN CARDIAC ARREST

Multiple Episodes of Ventricular Asystole with Survival

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BOSTON

EVALUATION of the proper method of therapy in cases of cardiac arrest or circulatory failure is difficult since many of the reported cases are not clinically analogous. The methods now in use include the injection of drugs directly into the heart, manual cardiac massage through an open incision and the use of various electric devices designed to defibrillate or to excite the cardiac musculature. The following case is reported in some detail to illustrate a variation in one of the more simple technics and to re-emphasize the value of an electrocardiographic diagnosis.

CASE REPORT

A. T. (M. G. H. 52521), a 70-year-old widow, entered the Emergency Ward on September 19, 1952, with the chief complaint of "fainting spells" for 2 days. She had first been seen in this hospital in 1937 because of chronic intermittent urticaria. In 1939 she was hospitalized for agranulocytic angina that was thought to have been due to aminopyrine. During this admission a psychiatric consultant made the diagnosis of paranoid personality on the basis of extremely hostile, secretive and suspicious behavior. Thereafter, she was seen in the outpatient clinics for the urticaria, and on numerous occasions diphenhydramine hydrochloride (Benadryl) was prescribed.

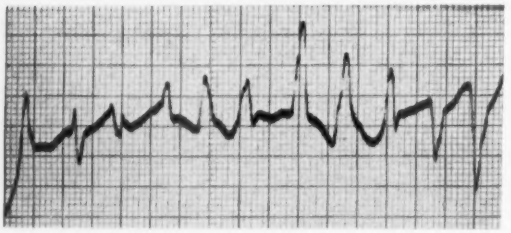

FIGURE 1. *Initial Electrocardiogram (Lead I), Taken before Any Medication Had Been Given.*

Two days before the present admission, the patient was suddenly seized by a sense of substernal oppression accompanied by consciousness of an irregular heart beat. She felt as though she were going to faint, but there was no pain. These symptoms recurred several times during the day and were usually accompanied by vomiting. The total duration of symptoms was 3 to 10 minutes for each episode. On the next day she lost consciousness twice after experiencing the same subjective symptoms. On the morning of admission she "fainted" seven or eight times and was seen by her physician, who sent her directly to the Emergency Ward. She was not given medication. She denied any previous neurologic symptoms. She stated that her blood pressure had been elevated for about 5 years and that for 2 months she had experienced shortness of breath on exertion. She also denied having ever taken any medication, even the much-prescribed diphenhydramine hydrochloride.

Physical examination revealed an elderly woman sitting upright in bed complaining that she was going to faint. A hostile, suspicious attitude was again noted. The skin was hot, moist and flushed. At times she uttered a loud cry, clutched at her chest, rolled up her eyes and seemed momentarily to lose consciousness. The blood pressure was 245/60, the respirations 24 to 34 per minute, and the apical heart rate 100 to 120, with a marked pulse deficit at the wrist. The rhythm was totally irregular. The neck veins were distended but did not pulsate. There was no edema. The heart was slightly enlarged, the border of cardiac dullness extending to the left, and the sounds were distant. The aortic second sound was greater than the pulmonic.

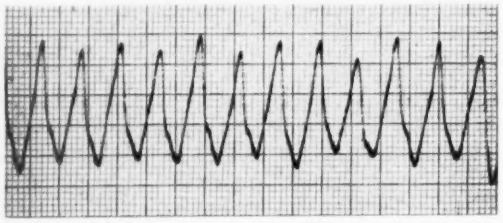

FIGURE 2. *Electrocardiogram (Lead I), Showing a Typical Episode of Ventricular Tachycardia.*

FIGURE 3. *Electrocardiogram (Lead I), during a Period of Ventricular Tachycardia just before the Onset of Ventricular Asystole.*

There was a Grade 1 apical systolic murmur without transmission. Examination of the lungs, abdomen and nervous system was unremarkable.

Examination of the blood revealed a hemoglobin of 13.5 gm. per 100 cc. and a white-cell count of 20,000, with a pronounced shift to the left. Stool examination was negative for occult blood. A voided urine specimen showed a +++ test for albumin, with 2 or 3 red blood cells, 4 white blood cells and occasional granular casts per high-power field in the sediment. The prothrombin time was 14 seconds. The serum carbon dioxide was 19.4 vol. per cent, and the sodium 143 millequiv. and the potassium 3 to 5 milliequiv. per liter; the nonprotein nitrogen was 34 mg. per 100 cc.

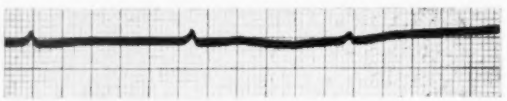

FIGURE 4. *Electrocardiogram (Lead I), Taken during Ventricular Asystole.*

An electrocardiogram taken before any medication was given showed a bizarre pattern of extreme ventricular irritability, with runs of ventricular tachycardia and ventricular fibrillation.

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During the next 24 hours the patient experienced 23 separate episodes of complete and prolonged ventricular standstill. In each the heart was made to beat again by the introduction of a cardiac needle into the ventricular wall. At no time was any medication introduced directly into the heart. During the first 12 hours efforts were made to influence the irritability of the heart by the use of various drugs. These included, in order, 0.4 gm. of quinidine sulfate by mouth given in the Emergency Ward, which was promptly followed by vomiting, 1400 mg. of procaine amide hydrochloride intravenously over a 5-hour period, 0.4 mg. of atropine sulfate intravenously and 0.4 cc.

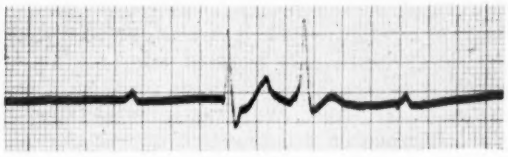

FIGURE 5. *Electrocardiogram (Lead 1), Showing Ventricular Systole after Cardiac Puncture.*

of 1:1000 epinephrine solution diluted to 1:500,000 intravenously. In no case did the use of these drugs favorably influence the frequency or severity of the attacks of asystole. Electrocardiograms (Fig. 1-6) of each attack during the entire 24-hour period were obtained. Gradually, the attacks subsided and did not recur. The patient was discharged on the 10th hospital day. When seen three months later she was doing well and had no cardiac symptoms.

DISCUSSION

It is of interest to examine the sequence of events during a typical attack of ventricular arrest and to correlate the clinical and electrocardiographic findings. The method employed to re-establish ventricular systole is also discussed.

Figure 1 shows the initial electrocardiogram taken before any medication had been administered. The ventricular patterns were bizarre and distorted from multiple ectopic foci; there were runs of ventricular tachycardia and fibrillation. The patient was alert, apprehensive and flushed without cyanosis. At the time of this tracing the blood pressure was high, and the peripheral pulses were strong.

Figure 2 demonstrates a typical run of ventricular tachycardia at a rate of 240. These episodes lasted from a few seconds to five or six minutes. At their beginning the patient clutched her chest and cried out. The eyes rolled up, the face became flushed, and respirations became deep and full. After thirty or forty seconds she became deeply cyanotic, and the apical heart sounds, peripheral pulses and blood pressure became unobtainable.

Figure 3 shows a period of ventricular tachycardia just before the onset of ventricular asystole. The voltages were markedly diminished, and the complexes were wide. By this stage spontaneous respiration had ceased, and there was no clinical evidence of life. This phase usually lasted ten to thirty seconds and ended with the abrupt onset of asystole. The configuration of the complexes suggested extreme ventricular fatigue.

Figure 4 indicates the period of ventricular asystole. The basic auricular rhythm was now evident at a rate of 55. These periods were allowed to continue from thirty to ninety seconds before definitive therapy was instituted, although artificial respiration was given at this time. The patient still showed no evidence of life except for the P waves visible on the electrocardiogram.

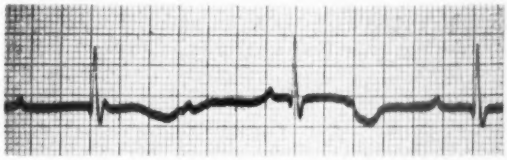

FIGURE 6. *Electrocardiogram (Lead 1), Showing Resumption of Cardiac Rhythm.*

After an interval of thirty to ninety seconds, during which there was no evidence of ventricular activity, a No. 22 cardiac needle was inserted into the fourth left intercostal space just to the left of the sternal border. An empty 2-cc. syringe was attached to the base of the needle for ease in handling, but no medication was introduced into the heart. During the first few attacks, simple puncture of the anterior ventricular wall was sufficient stimulus to cause resumption of the heart beat. When this became apparent the needle was withdrawn. During the majority of the attacks, however, this procedure failed to result in ventricular systoles. In these episodes the needle was advanced into the chamber of the ventricle and its position checked by the withdrawal of a few cubic centimeters of blood. It was then advanced until resistance was met, presumably from the endocardial surface of the posterior ventricular wall. When the syringe was struck lightly with the fingers, a ventricular systole was produced. The operator was able to produce single contractions or runs of two or three contractions at will. It was thus possible to maintain ventricular systole at a set rate for several minutes. Artificial respiration was maintained throughout the period. When either the operator or his assistant at the electrocardiogram became aware of spontaneous ventricular systole, the needle was withdrawn. Figure 5 demonstrates two ventricular systoles produced in the manner described above. After a short interval the patient's respiratory activity returned, and she regained consciousness and was able to talk. She had no memory of any of the twenty-three cardiac punctures.

After twenty-four hours of repeated attacks, the cardiac rhythm settled down to the pattern shown in Figure 6, and no further attacks occurred. An electrocardiogram taken on the fifth hospital day disclosed third-degree auriculoventricular block,

with ventricular patterns suggesting right-bundle-branch block. The patient was discharged on the tenth hospital day ambulatory and without cardiac symptoms.

The cause of this woman's cardiac irritability and repeated standstill remains a matter of speculation. A toxic phenomenon was suspected at the outset. It was not possible to support a diagnosis of myocardial infarction on either clinical or electrocardiographic grounds. Among her effects were found numerous compounds, all containing diphenhydramine hydrochloride, but no digitalis. The possible toxic effects of the diphenhydramine hydrochloride were investigated. Of the many cases reported in the literature, none showed an entirely similar clinical picture to this case. Nevertheless, such subjective sensations as "suffocating attacks," palpitation and dyspnea have been described. In addition tachycardia, cyanosis, coma, hypertension, and circulatory collapse have been attributed to the drug. Electrocardiographic changes, including increase or decrease in height of QRS complex, ST-segment and T-wave changes and increases in the PR interval, have been reported. Since the patient would not admit taking even the diphenhydramine hydrochloride contained in her multiple outpatient prescriptions, no conclusions about the part played by this drug are warranted.

In the case presented above, and 2 others that I have observed, periods of asystole were preceded by prolonged periods of ventricular tachycardia. Because cerebral anoxia developed gradually, the patients passed through the clinically discernible phases described. The case reported above also suggests that varying degrees of mechanical stimulation are possible, depending on where and to what extent the myocardium is irritated. It is quite possible that the introduction of the cardiac needle alone accounts for the apparent therapeutic success in some cases.

It is difficult on clinical grounds alone to distinguish one form of cardiac catastrophe from another. It is equally difficult to decide which form of emergency therapy is appropriate in a given case. With the exception of accidents that occur in the operating room, where the situation is better controlled and the patient known to the operators, most acute cardiac catastrophes occur under far from ideal conditions and yet demand immediate action. Ventricular tachycardia, ventricular fibrillation, asystole and the extremes of circulatory collapse are clinically similar. Intracardiac puncture is a quick and simple procedure that can be initiated while arrangements are being made for any of the more radical forms of treatment. Furthermore, the opening of the chest in persons with severe heart disease may in itself preclude the possibility of recovery. Likewise, this procedure will be to no avail if the patient is later found to be suffering from repetitive Adams-Stokes seizures or from recurring attacks of ventricular asystole over a prolonged period as in the case reported above. It is also appreciated that electric devices cannot be used rationally without an electrocardiographic diagnosis or direct visualization of the heart. With these considerations in mind, it might be well to regard the use of cardiac puncture without medication as a quickly available preliminary procedure in the "unknown" case while the necessary equipment and personnel are being mobilized for more accurate diagnosis and treatment.

Summary

A case of recurring ventricular asystole is presented in which the heart was made to beat again repeatedly by mechanical stimulation with an intracardiac needle. The clinical and electrocardiographic findings are compared. The possibility that diphenhydramine hydrochloride was the causative agent is briefly discussed. The value of mechanical stimulation of the heart with an intracardiac needle, even without the use of intracardiac drugs, in the treatment of acute cardiac standstill is suggested.

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THE FRACTURE BLISTER*

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THERE is no mention in the dermatologic literature of the occurrence of vesicles or bullae (Fig. 1) secondary to fractures, and localized to the site of injury. The fracture blister may be noted before application, or after bivalving of a plaster cast. The lesion is usually produced by direct trauma. It is always associated with severe soft-tissue injury and an embarrassed circulation at the fracture site. Certainly, all orthopedists, general surgeons and general practitioners are familiar with the lesion from the clinical point of view because trauma and its care are distinctly in their province. Bullae, occurring as an epiphenomenon, although of great interest to the dermatologist, necessarily become of secondary import, and rarely does he have an opportunity of even seeing such lesions. Actual treatment of the lesion by the surgeon is variable (Table 1), and the lesions may, at times, serve as a deterrent to open-reduction procedures. The purpose of this paper is to study the histopathology of the formation and healing of the bulla so that definite treatment may be outlined, and to call the attention of dermatologists to the lesion.

Ten cases of fracture were selected for the study (Table 1). The salient clinical features noted in the selected cases may be summarized as follows: the patients, whose ages ranged from eighteen to sixty-three years, were predominantly male (9 out of 10 cases); the fracture was usually of the distal third of the leg and usually simple but was associated with considerable soft-tissue injury (the blister may also occur with compound fractures); the fracture blister may be noted clinically as early as twelve hours after trauma, or may occur as late as the twenty-fifth day (new blisters may be noted daily over a period of ten days); whether reduction was carried out promptly or delayed did not seem to influence the occurrence of the fracture blister.

TABLE 1. *Pertinent Data in 9 Cases of Fracture Blister.*

PATIENT	AGE	SEX	TYPE OF FRACTURE	SOFT-TISSUE INJURY	INTERVAL BEFORE FRACTURE BLISTER FIRST NOTED CLINICALLY	IMMEDIATE TREATMENT GIVEN FRACTURE	ACTUAL TREATMENT OF FRACTURE BLISTER
	yr.				days		
F. H.	32	M	Simple (both bones, middle third, left lower leg)	++++	2	Cast applied within 24 hr.	Incision and drainage; vaseline gauze.
W. S.	31	M	Simple (both bones, middle third, right lower leg)	++	1 (new blisters formed over 9-day period)	Cast applied within 24 hr.	None
C. Q.	59	M	Simple (both bones, distal third, right lower leg)	+++	4 (noted under bivalved cast)	Cast applied within 24 hr.	Vesicle unroofed; epidermis normal after 15 days.
M. W.	47	F	Simple (trimalleolar, with posterior dislocation of right foot)	+++	6 (noted under bivalved cast)	Cast applied within 12 hr.	None; epidermis normal after 14 days.
W. F.*	40	M	Simple (both bones, distal third, left lower leg)	++++	25	Cast applied on 27th day	Vesicle unroofed; dry sterile dressing applied; epidermis normal after 43 days.
D. S.	33	M	Compound (both bones, distal third, left lower leg)	++++	3 (noted under bivalved cast)	Cast applied within 6 hr.	Vesicle unroofed; dry sterile dressing applied; epidermis normal after 11 days.
P. G.	54	M	Simple (left os calcis)	+++	1	Cast applied on 8th day	Vesicle unroofed; West compress for 5 days, followed by application of cast.
C. S.	42	M	Simple (both os calcis)	+++	3	Cast applied on 11th day	Vesicle unroofed; wet compress applied.
P. K.	18	M	Simple (bimalleolar, right ankle)	+++	3 (2d blister noted on 10th day)	Cast applied within 3 hr.; reapplication of cast on 16th day.	Vesicle unroofed; bismuth tribromphenate gauze applied; epidermis normal after 10 days.
W. M.	63	M	Simple, oblique (external malleolus of right ankle)	++++	½	Cast applied on 7th day	Vesicle unroofed; dry sterile dressing applied.

*Patient sustained multiple injuries. Course complicated by development of bronchopneumonia and thrombophlebitis.

HISTOPATHOLOGY

Figure 2 presents an intact bulla whose surface is composed of a normal corneal layer overlying markedly compressed epidermal cells. The contents of the bulla are acellular and are made up of amorphous, pink-staining material. Approximately

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three quarters of the floor of the bulla is situated at the dermoepidermal junction. The portion

FIGURE 1. *Large Fracture Blister of the Left Ankle (Patient C. S.) Containing Hemorrhagic Fluid (Noted When the Cast Was Bivalved Five Days after Application).*

demarcated by the arrows is lined with a layer of compressed epidermal cells. The cutis beneath the

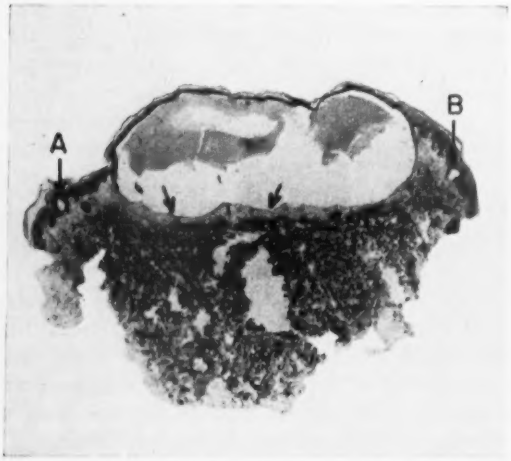

FIGURE 2. *Skin Punch Biopsy Specimen, 4 Mm. in Diameter, of an Intact Blister, Taken Twelve Hours after Injury in Patient W. M. (Histologic Paraffin Section, Hematoxylin and Eosin Stain X27).*

Arrows demarcate the single layer of compressed epidermal cells. Note the tiny vesicles at A *and* B.

bulla is markedly edematous and contains many extravasated red blood cells.

The blood vessels of the middle and lower cutis disclose a moderate to marked perivascular infiltrate consisting chiefly of polymorphonuclear

FIGURE 3. *Skin Punch Biopsy Specimen, 4 Mm. in Diameter, Taken Ten Days after Injury from Patient D. S. (Histologic Paraffin Section, Hematoxylin and Eosin Stain X27).*

leukocytes and lymphocytes. An occasional vessel shows an endarteritis.

FIGURE 4. *Higher-Power Magnification of Section A of Figure 3 (X70).*

The sweat-gland structure appears normal. The glands, however, are surrounded by a moderate to marked infiltrate consisting chiefly of polymorphonuclear leukocytes and lymphocytes.

The vesicle situated at *A* has two layers of compressed epidermal cells for its floor. The vesicle situated at *B* has the lateral half of its floor situated at the dermoepidermal junction.

Figures 3 and 4 demonstrate a necrotic lamina of epidermis overlying a bulla that contains red blood cells and amorphous, pink-staining débris. There is a complete epidermal layer beneath or on the floor of the bulla. There is slight edema at the dermoepidermal junction. Many of the epidermal cells show a vacuolated cytoplasm. The blood vessels and the sweat glands appear normal.

Discussion

In the sections studied, the marked edema that accumulated rapidly after the injury caused the epidermis to be elevated at the dermoepidermal junction. There were no intercellular or intracellular changes within the epidermis, nor was there any acantholysis, as may be noted with some bullous dermatoses. Rather, the histologic findings observed in the earliest clinical lesions were reminiscent of those noted experimentally by various technics employed in the production of dermoepidermal separation.[1-8] In the fracture blister, however, a single layer of compressed epidermal cells was usually noted in a segment of the floor of the bullae. These cells served as the nidus in the regeneration of the epidermis, along with those on either margin of the bulla at its adjacent skin level. The finding is confirmed clinically in that scarring subsequent to healing of fracture blisters is extremely rare.

The rate of healing of the epidermis underlying a fracture blister depends on the size of the bulla, retention of epidermal cells on its floor to serve as a nidus and its dermal blood supply. From sections of the lesions studied histologically, it may be shown that when its size has been constant for approximately five days, treatment may consist of unroofing and application of a dry sterile dressing.

Clinically, although fracture blisters seem to occur more frequently on the lower extremities, they may occur in any location, in any age group, and in either sex when the fracture is produced by direct trauma, and the intervening soft tissues are severely contused.

Summary

Ten cases of fractures with concomitant fracture blisters are discussed.

Histologic studies on the formation of early clinical lesions and on the healing of older lesions are described. Treatment determined by histologic study of clinical lesions is outlined.

The fracture blister is presented as a dermatologic entity.

We are indebted to Drs. O. Sherwin Staples and Stuart Russell, of the Orthopedic Department, Hitchcock Clinic, for making available the records of the cases included in this study.

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GLUCOSTATIC MECHANISM OF REGULATION OF FOOD INTAKE*

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THE regulation of energy intake is fundamental to all homeostatic mechanisms. Yet this basic process has received less attention than many of the physiologic regulations that it makes possible.

Before this century, three theories were advanced to account for the phenomenon of hunger. The theories of peripheral origin (Haller, Erasmus Darwin, Johannes Müller and Weber) held that the taking of food resulted from the stimulation either of all afferent nerves by some change in the tissues or of a strictly local group of sensory nerves, mainly in the stomach. The theory of central origin (Magendie, Tidewald and Milne–Edwards) postulated that a hunger center was sensitive to a starvation state of the blood. The theories of general sensation (Roux and Michael Foster) considered that the hunger center of the blood was stimulated not only by the hunger state of the blood but also indirectly by afferent impulses from all organs of the body.

After Cannon and Washburn, as well as Carlson, had shown that epigastric sensations of "hunger pain" coincided with waves of contractions of the empty stomach, Carlson[1] suggested that hypoglycemia, mediated by its effect on the stomach, might be responsible for inducing these hunger sensations. Although hunger pangs are found in most persons, the idea that the sensations elicited

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by stomach contractions due to hypoglycemia[2] were at the basis of the regulation of food intake was abandoned for the following reasons: it was repeatedly shown, in particular by Sherrington, that total denervation and surgical removal of the stomach did not fundamentally alter the characteristics of food intake regulation. Adolph[3] demonstrated, by diluting the ration of laboratory animals with inert material, that differences in the bulk of the diet had only a transient influence. Scott and his collaborators[4] were unable to correlate spontaneous fluctuations of blood sugar levels with a desire for food. The existence of diabetic hyperphagia and of the phenomenon of hunger diabetes also presented seemingly insurmountable difficulties. Even the increase in spontaneous intake due to insulin-induced hypoglycemia was held by some authors to be of no general significance because of the abnormal "unphysiologic" circumstances in which the organism was placed.[5]

The demonstration by Hetherington and Ranson[6] that destruction of parts of the medioventral nuclei of the hypothalamus leads to obesity and the work of Anand and Brobeck[7] showing that more lateral lesions cause anorexia reopened the problem of the nature of the physiologic mechanism of the regulation of food intake.

Experimental work on rats, mice, dogs and human subjects culminated in the proposal of a "glucostatic mechanism" of regulation of food intake.[8-10] The initial reasoning was as follows: the regulation of food intake proceeds by relatively frequent partaking of food (meals). It appears improbable that hypothalamic centers are sensitive to decrease of the body content in fat or protein — during the short interval between meals, this decrease is proportionally very small. On the other hand, the body stores of carbohydrate are limited. The postprandial liver glycogen content in man is approximately 75 gm. — only 300 calories' worth. In the postabsorptive period, in spite of gluconeogenesis (the synthesizing of glycogen from body proteins), glycogen stores become rapidly depleted. This synthesis of glycogen from proteins and the shifting of metabolic oxidation in non-nervous tissues from glucose to fat (as measured by the lowering of the respiratory quotient) tend to minimize the drop in blood glucose resulting from depletion of liver glycogen stores. Thus, minimum levels necessary for the survival of the central nervous system are maintained. Only partaking of food, however, can restore full homeostasis of the central nervous system. It appeared, as a working hypothesis, that the central nervous system, dependent exclusively on a continued supply of glucose in blood, should maintain "glucoreceptors" sensitive to fluctuations of available blood glucose. (That glucoreceptors do in fact exist in the central nervous system has been implicitly recognized by surgeons; a common method for testing the completeness of vagotomies consists in administering insulin and ascertaining that the resultant hypoglycemia fails to elicit or delays gastric secretion of hydrochloric acid.)* In this "glucostatic" view, hunger would be integrated among the mechanisms through which the central nervous system ensures its homeostasis.

A first (and rather crude) test of this hypothesis was provided by a systematic survey of the effect of administration of various metabolites[9] on the food intakes of groups of normal animals. Increases in levels of reducing sugar in blood were obtained by injections of glucose or fructose or small doses of epinephrine. Decreases were obtained by injections of small, graded doses of insulin. Levels below normal fasting values were avoided, so as to stay within physiologic limits. The effects of the injection of substances without influence on blood glucose levels, like sucrose and fat emulsions, were also studied. It was found that temporary increases in blood glucose levels corresponded to decreases in food intake and vice versa, even when the caloric equivalent of injected metabolites was taken into account. Substances without effect on blood glucose did not influence food intake over and beyond caloric value, if they were metabolizable. Although significant, variations in food intake induced by these variations in blood sugar were small because of the efficiency of homeostatic mechanisms concerned with blood glucose levels. To demonstrate more clearly the inhibitory effect of high blood glucose levels on food intake, animals of the "Houssay" type, in this case alloxan-treated hypophysectomized rats, were injected with glucose.[9] (Although these animals do not normally present hyperglycemia, they have been deprived of the mechanisms that ensure the rapid removal of injected glucose; hyperglycemia can thus be conveniently maintained for a much longer period.) Two daily glucose injections were found to reduce food intake by half; three such injections, maintaining hyperglycemia around the clock, caused death of these animals from inanition in spite of the presence of food in their cage.

The apparent paradoxes afforded by the hyperphagia of diabetes mellitus, by the phenomenon of hunger diabetes, in which a previously fasted person will continue to eat in spite of a blood glucose reaching abnormally high levels, by the hyperphagia accompanying tendency to higher glucose levels in the obese, still had to be resolved before it could be concluded that blood glucose levels regulate food intake. It appears that all these conditions may have one factor in common — namely, that whereas absolute levels of blood glucose are increased, utilization is decreased. For variations of blood sugar levels to influence hypothalamic glucoreceptors, glucose has to cross the mem-

*This phenomenon was recently analyzed experimentally by Porter et al.[11] It was shown specifically that in monkeys the anterior hypothalamus was responsible for the secretion of hydrochloric acid after insulin administration.

branes of these cells. This presumably implies phosphorylation through the hexokinase reaction. If phosphorylation is impaired, "effective sugar levels" will be in fact lower than absolute values as measured.

This concept was tested and put on a quantitative basis in a series of experiments performed on human subjects.[10, 12] Because of the inaccessibility of the hypothalamic centers, peripheral arteriovenous differences were determined as an index of rates of glucose utilization. These differences (designated as "Δ-glucose") were measured in the antecubital region (between finger blood and antecubital-vein blood). With one exception, discussed in some detail below, Δ-glucose values were found to correlate closely with the caloric intake of the subject and with hunger feelings (Fig. 1).

Diets calorically adequate were associated with Δ-glucose values that remained large[8] throughout the day, decreasing only at mealtime. By contrast, submaintenance diets were followed by rapid shrinkage of Δ-glucose after meals; at the same time, hunger returned. When hunger diabetes was present, blood glucose values rose until a difference appeared between arterial and venous levels—only then was hunger assuaged. Generally speaking, there appeared to be a quantitative relation between food intake and the area represented by the Δ-glucose as a function of time. There was also a quantitative relation between Δ-glucose values and the incidence of hunger feelings; antecubital arteriovenous differences of more than 15 mg. per 100 cc. were never associated with hunger; values staying near 0 for any length of time were always associated with hunger.

In uncontrolled diabetes mellitus, a similar picture was obtained; blood sugar values had to be forced up through ingestion of food to levels where arteriovenous differences were introduced for ravenous hunger feelings to be satisfied. Cortisone administration accompanied by increased appetite caused an elevation of absolute glucose levels but a decrease in Δ-glucose.

The effect of epinephrine deserves special mention since it represents an apparent exception to the general rule. Administration of epinephrine caused an immediate increase in blood glucose; it drastically reduced or eliminated any effect of hunger. However, at the same time, it decreased peripheral Δ-glucose to levels near 0. Although it may be an oversimplification to ascribe this seeming contradiction to one of the many physiologic effects of epinephrine, it is worth noting that epinephrine introduces a differential between peripheral and central blood flow.[13] By the same token, experiments conducted on animals demonstrate that, whereas it decreases peripheral Δ-glucose values, it increases carotid-jugular glucose differences; thus it not only produces hyperglycemia but also increases the proportion of glucose made available to the nervous centers.*

Insulin treatment first causes a fall in blood sugar owing to increased peripheral utilization of glucose. In a second phase, a compensatory rise takes place that is secondary to decreased utilization of glucose in the periphery.[15] Delta glucose values rapidly decline when the blood sugar falls to or below post-absorptive levels. The occurrence of increased hunger after insulin administration is therefore easily interpreted if hunger is seen as a direct response to carbohydrate deprivation.

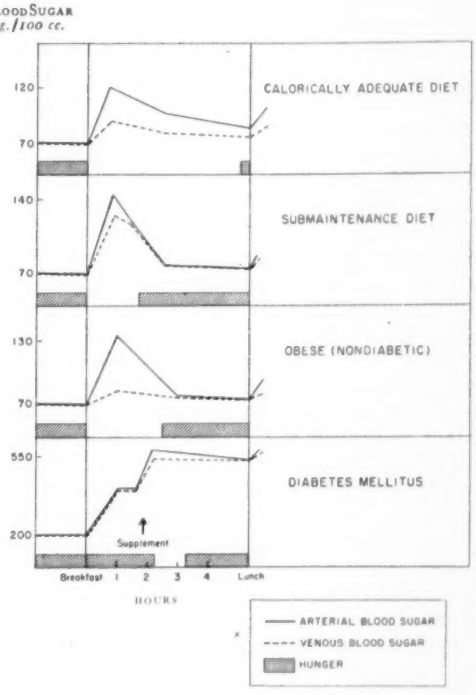

FIGURE 1. *Typical Morning Correlations of Δ-Glucose and Hunger Feeling.*

The size of the Δ-glucose (peripheral glucose arteriovenous difference) correlates with hunger feelings. No hunger feeling appears if the Δ-glucose is greater than 10 mg. per 100 cc.

In hyperthyroidism, alimentary hyperglycemia typically occurs and is followed regularly by a postalimentary hypoglycemia. It has been suggested[16] that accelerated metabolism of glucose takes place in the hyperthyroid patient and that the alimentary hyperglycemia may be only a manifestation of starvation diabetes that follows rapid depletion of carbohydrate stores. It appears that the metabolic hypoglycemia of hyperthyroidism

*Keller and Roberts[14] recently demonstrated that glucose consumption of hypothalamic tissue is increased in vitro within a few minutes of the administration of epinephrine.

may thus be related to the increased food intake characteristic of this condition.*

The possibility that the "feeding centers" in the lateral hypothalamus represent the sensitive area with facilitatory properties in terms of eating mechanisms has been discussed by Brobeck.[18]† In the glucostatic view proposed here these centers would represent the glucoreceptors. There is an obvious need for a mechanism that would translate available blood glucose into variations in the physiologic state of the tissues. Such a mechanism is suggested by the observation that a drop in serum inorganic phosphate and in potassium consistently accompanies large Δ-glucose values.[12, 20, 21] It is possible that the passage of potassium ions into the glucoreceptor cells along with the glucose phosphate represents the point at which effective glucose level is translated into an electric or neural mechanism.

It is recognized that hypothalamic impulses still have to be interpreted, integrated and acted upon by the cerebral cortex; that other afferent impulses (gastric hunger pangs, in particular) also play a role in determining conscious states of hunger; and that other psychologic and physiologic factors may intervene to modify appetite at least temporarily. Conditioned reflexes, particularly in the dog, and habits in man also play an important role. Still, although feelings involving desire for food or satiety are not in any sense quantifiable, they represent a conscious expression of one of the most precise regulatory devices in biology. The glucostatic mechanism suggested here seems to provide a basis for such a precise regulation. It may be added that, because of the established decrease by available glucose of the rate of fat[22] and amino acid[23] utilization in non-nervous tissue, and probably of the rate of gluconeogenesis as well,[24] the regulation of food intake is easily integrated into the general regulation of metabolism.

Finally, it may be noted that the glucostatic theory seems to permit interpretation of certain types of alteration of the regulation of energy intake, in particular hypothalamic obesity,[25] the hereditary obese hyperglycemic syndrome of mice[26] and at least one form of human obesity.[27] The demonstration[28] that, in the hereditary obese-hyperglycemic syndrome of mice, the alpha cells of the islands of Langerhans oversecrete a hormone with hyperglycemic, glycogenolytic and antiinsulin properties opens the possibility that this hormone plays a major role in the regulation of food intake and in the etiology of obesity.

The broadening of the initial theory and its application to special cases were evolved in collaboration with Dr. T. B. Van Itallie, for two years a member of the Department of Nutrition, Harvard School of Public Health, and now at St. Luke's Hospital, New York City. The work summarized here was done with the collaboration of Dr. Rachel Beaudoin, a former graduate student in the Department, now at the University of Montreal, and of Miss Margaret Bates, also a graduate student. I am also indebted to Dr. Fredrick J. Stare, head of the Department, for his constant support, interest and encouragement.

*It has recently been shown[17] that, in the cold, carbohydrate metabolism is also accelerated and glycogen reserves are decreased. A similar situation is known to prevail in growth.

†It was later demonstrated that electric stimulation of this lateral area causes an increase in food intake.[19]

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MEDICAL PROGRESS

CHANGING CONCEPTS IN THE SURGERY OF CANCER*

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"IN estimating the limitations of surgery we find none except they be set by ourselves. How shall they be set? By conservative judgment opposed to rashness." This estimate of "The Future of Surgery without Limit" was made by David W. Cheever[1] in his presidential address to the American Surgical Association before the turn of the century. Sixty-four years later it has a singular applicability to the surgery of cancer.

The surgeon of today, as Cheever foresaw, is enabled by virtue of the technical advances of his art to carry out an operation of almost unlimited extent. In dealing with cancer, however, he is seriously handicapped in setting the extent of a procedure by an almost total ignorance of the biologic propensities of the lesion he is attempting to treat. The most radical operation on a seemingly early lesion may be followed by widespread, rapidly progressive metastases and, contrariwise, a palliative resection undertaken with no hope of permanent cure may result in an extraordinarily long period of well-being for the patient. Until an accurate appraisal of the growth potentialities of any given tumor can be made, the surgeon must continue to grope in comparative darkness. In this darkness, however, there are rays of light, the perception of which will be enhanced by a distinct change in the traditional concept of the nature of cancer. This change in concept is of more than philosophic importance to the surgeon.

Theoretical Considerations

Traditional notions regarding cancer, which have become so ingrained that they seriously hamper the judgment of the surgeon in its treatment, may be summarized as follows: first, cancer is a lawless, autonomous growth that spreads constantly and progressively throughout the life of the host and is dependent upon the host for its blood supply alone; secondly, early treatment is synonymous with cure and, conversely, late treatment is of little or no avail; finally, there is a close correlation between the histologic structure and the biologic behavior of neoplasms.

Evidence against the Autonomy and Constant Progressive Growth of Cancer

The wild, destructive, continuous and purposeless growth of many tumors has led to the belief that neoplasia is an autonomous process. In this sense a cancer is a parasite that destroys the host on which it depends only for its blood supply. This view was supported by Ewing[2] and has been widely accepted. From a practical point of view, it allows for no alteration in tumor growth except by its direct destruction.

This thesis has been recognized as untenable by a number of pathologists for many years.[3] The orderly cellular pattern and obvious functional activity of certain cancers, particularly of endocrine glands, is against this view. The rare regression of distant metastases after removal of a primary tumor or after castration in ovarian lesions has been recognized for many years. Such a prolonged quiescence or even regression of malignant growth can hardly be ascribed to inadequate blood supply and suggests dependence upon some metabolic factor derived from the host.

Convincing evidence of the dependence of certain neoplasms on the metabolism of the host has been provided by the studies of Huggins and others on the regression of prostatic carcinoma after orchidectomy and adrenalectomy.[4-7] The alterations of the growth pattern of cancer of the breast by androgens and estrogens is additional evidence that the metabolism of cancer cells may be altered by indirect measures.[8-12] Although many years may elapse before similar changes can be induced in other cancers, the implications are obvious, particularly in relation to avenues of research in cancer.

One of the most widely accepted characteristics of cancer is that the rate of growth is constant for each tumor. Part of this belief is based on the histologic structure of particular neoplasms, which tends to remain fairly constant throughout the life of the host. The most convincing evidence, however, is that the life space of the host with an untreated tumor is remarkably similar for lesions in specific organs. Shimkin[13] has collected statistical data from several sources that show, for example, that in cancer of the esophagus nearly all the patients die within three years. In cancer of the breast, on the other hand, over 20 per cent are alive at the end of five years. The rate varies for other lesions such as carcinoma of the bladder, rectum and cervix. But in general, the data indicate that the life span of hosts with tumors in particular locations is sufficiently similar to suggest a true correlation.

These data do not, however, exclude the possibility of great variations in the rate of growth during the career of any particular tumor. Thus, an

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untreated cancer of the rectum that kills the host at the end of three years falls within the anticipated survival curve of cancer of the rectum, but careful observation of the patient during this period may indicate that for the first two and a half years the tumor had remained comparatively quiet and then had grown at an extraordinarily rapid rate during the last six months of the patient's life. Certainly, clinical observations of patients with advanced cancer strongly suggest that variations in the rate of growth within the life span of the host are extraordinarily common. This is particularly characteristic of recurrent and metastatic lesions. Indeed, the vast majority of metastatic lesions that appear several years after the removal of primary tumors must be interpreted as showing evidence of a significant period of quiescence since they must have been present at the time the original lesion was excised.[14-16] A case has been described in which at reexploration four and a half years after excision of a large recurrent cancer, no evidence of neoplasm could be found within the abdominal cavity.[17] Yet six months later, the patient was dead from extensive abdominal carcinomatosis. A second primary lesion could not be demonstrated. Although the logarithmic character of tumor growth accounts in part for the apparently more rapid progression as a tumor increases in size it does not explain such a long period of quiescence as occurred in this case, in which no evident progression of the lesion could be demonstrated.

It is particularly important to realize that the rate of growth of metastatic lesions varies in different locations. This phenomenon is readily seen in the skin metastases of cancer of the breast. A new lesion may appear and grow with extraordinary rapidity at a time when an earlier adjacent lesion remains exactly the same size or is regressing. Scott[18] described a patient with cancer of the prostate in whom successive crops of skin metastases appeared and regressed completely without therapy. Cases of metastatic cancer in which the rate of growth varied widely in different locations have occurred.[19]

The most remarkable evidence of fluctuations in the growth of malignant neoplasms is seen in the rare but significant cases of spontaneous regression. In 1918 Rohdenburg[20] collected 100 such cases from the literature. More recently, similar cases have been described by Rae[21] and Dunphy.[19] Duke-Elder[22] believes that there are at least 11 well authenticated cases in which spontaneous cure of malignant retinoblastomas of the eye has occurred. Prolonged quiescence of malignant melanomas are well known, and there are rare but well documented cases of spontaneous regression of this disease.[23,24]

A significant point to be made about these retrogressions of tumor and variations in the growth of metastatic lesions lies not in the hope that it offers the patient but in the evidence that it provides of the susceptibility of malignant growths to systemic and local factors arising within the host.

Significance of Time in the Treatment of Cancer

The traditional concept of cancer reveals it as a mutation of cells arising in a single microscopic location and steadily expanding in accordance with a specific rate of growth; after reaching a certain size, which varies with different tumors, it spreads through lymphatic channels to regional nodes. After being temporarily arrested by lymph nodes, the neoplastic lesion extends into neighboring structures and finally enters the blood stream, where it produces distant metastases. Accordingly, effective treatment merely should be carried out early enough, which means before the lesion metastasizes to distant areas, preferably before it spreads to regional nodes and ideally while it is still a microscopic nest of cells. According to this theory, time is the essence of cancer therapy. In rapidly growing, undifferentiated lesions there is little time during which successful therapy may be accomplished; in slowly growing lesions there is more time, but theoretically, if all cancers were detectable early, the cure rate would approach 100 per cent.

Apart from the fact that this traditional concept cannot be supported by the available evidence, it has one serious and dangerous consequence. Overemphasis of the importance of early treatment is blinding clinicians to the fact that many large, so-called "late cases" are amenable to successful treatment. This is particularly true of cancer of the gastrointestinal tract in patients in the older age group. I have heard it argued in view of the recognized poor salvage rate in gastric cancer, that resection of a large gastric tumor in an old man was unwarranted, because in the particular case under discussion "the story was of such long duration and the tumor so large that it must have metastasized." How many patients have been deprived of the benefit of a surgical opinion on this basis is a matter of conjecture.

Although there are tumors that in their behavior adhere faithfully to the traditional ideas of cancer, the spectrum of growth is so wide and variable that a radical revision of this concept is essential.

In the first place it is of more than theoretical importance for the surgeon to know that the unicentric, microscopic, single-focus, one-cell or two-cell origin of cancer is no longer tenable. There is abundant evidence that neoplasia arises from fields of tissue and enlarges not merely by cellular proliferation but also by progressive neoplastic conversion of tissue within these fields.[25,25-27] Multicentric or large field origin of cancer is particularly characteristic of cancer of the skin, breast, pancreas, prostate and gastrointestinal tract.

Regardless of the mode of initial carcinogenesis the variations in growth potential are extraordinary. Some tumors must begin to metastasize while the initial focus of tumor is still microscopic. Others may be confined to a local area for months or years. The extremes of the spectrum are familiar to every experienced clinician. A huge, solitary metastasis from a small focus of tumor in the thyroid gland or in the kidney may be contrasted with the prolonged local invasion of a comedo cancer of the breast. Although these extremes are recognized, the frequency with which the biologic propensities of the cancer outweigh any advantage to be gained by early treatment is not appreciated. It is a discouraging fact that with the exception of certain cancers, notably of the cervix and the skin, there is little difference in five-year survival rates in groups of patients treated within the first few months of the onset of symptoms and in those treated after delays as long as a year. This has been demonstrated in studies of cancer of the stomach and ovary, certain series of cancer of the breast and in osteogenic sarcoma.[28-30]

One must not conclude from these data that time is of no importance. It is quite obvious that a patient who is cured after a resection of a large carcinoma of the rectum that has been present for two years would have been better and more effectively treated with less risk to life had the operation been performed one and a half years earlier. Moreover, although it is unlikely that the earliest possible treatment will alter the ultimate cure rate in highly malignant neoplasms, it unquestionably increases the months or years of salvage given to that patient. Early treatment will always be a desideratum, but it is not the *sine qua non* of successful therapy. The same emphasis that is placed upon the factor of time must also be given to a better understanding of the complex biologic nature of this disease, particularly the wide variations in growth patterns, the great disparity in behavior of different tumors and of the same tumor in different locations and the possible role of natural defenses arising within the host.

Histology as an Index of Biology

Morbid histology has helped so much to place surgery on a rational basis that surgeons are apt to accept the interpretation of a pathologist at more than its face value. The penultimate classification of tumors undertaken by some pathologists is particularly misleading because it implies a close correlation between the histologic appearance of a tumor and its biologic behavior. Actually, no such correlation exists. When the pathologist looks at a section from a particular tumor and classifies it as "highly malignant" or "carcinoma simplex, Grade 3," he knows nothing about the biologic propensities of the tumor in question. He merely means that, in his experience or according to what he has read, a majority of tumors, conforming more or less to this histologic appearance, have proved to be highly malignant in the past. There is no doubt that generally the more anaplastic a tumor appears histologically, the more highly malignant it is likely to be. However, there are so many exceptions to this general rule that no precise predictions are warranted. The discrepancy is so great that treatment should never be withheld or altered solely on the histologic appearance of a tumor. Thus, the pathologist who looks at a section of a metastatic thyroid tumor with well differentiated follicles might be hard pressed to make a diagnosis of malignant growth; conversely, when confronted with a benign melanoma from a child, he might advocate amputation if he were not familiar with all the related circumstances. Histology is a guide to the probable biologic potentialities of a tumor, but it must be carefully correlated with the origin of the tumor, its size and the known duration of its presence. In planning the therapy of cancer the surgeon is largely involved in balancing probabilities, and the histologic appearance of the tumor should be given no more than its proper weight.

Practical Considerations

Up to the present moment changing concepts of the nature of cancer have produced no advance of revolutionary significance in the surgery of this disease, but several avenues of research that have opened should be mentioned. The first of these is a renewed interest in the old idea that there are natural defenses against the growth of tumors.[31-33] A second is a search for a biologic indicator of the growth potentialities of tumors,[34-37] and a third is the study of the hormonology of neoplasia, particularly the relation between pituitary-adrenal function and the growth of cancer of the breast and prostate.[38,39] No attempt to cover the voluminous literature that has sprung up in this field is made in this review. Suffice it to say that from the point of view of the surgeon the most acute need is a rapid method of assaying the growth characteristics of each tumor before operation. The advantages to be gained are so obvious that they require no elaboration, but what a boon it would be to know that in a particular cancer multiple distant metastases had already occurred or were inevitable and that a limited surgical procedure was indicated—or to know that a radical resection of the chest wall and mediastinal lymph nodes was fully justified because the nature of a particular cancer of the breast was such that if a radical extirpation of the nodal spread could be accomplished, a cure would be assured! Indeed, by this means the place of all superradical resections for cancer could be pin-pointed, and their permanent place in the surgeon's armamentarium established. Until this kind of knowledge becomes available, however, the surgeon must continue to balance probabilities in his selection of operative procedures

for cancer, and it is to a consideration of this problem that the rest of this review is directed.

According to the traditional concept of cancer, surgery, if it is to be effective, must only be applied early and be sufficiently radical to encompass the spread of the disease. "How radical?" is the question that continually besets the surgeon, and a growing dissatisfaction with the results of surgery is leading to the development of more and more extensive procedures. In fact, the current trend in the surgery of cancer may be compared with the behavior of a savage who has learned how to extract nails with a hammer. He knows that the larger the nail, the harder he must pull. He has had no experience with screws, however, and so long as he is dealing with nails, the results are quite satisfactory, but when he is confronted with a screw, his efforts succeed only by shattering the wood. The surgeon is in fact a step worse off since too frequently he shatters the patient but fails to extract the cancer.

How, then, should the limitations of surgery for cancer be set? Until more accurate means of appraising the biologic propensities of a particular tumor become available, the answer can only be "by conservative judgment opposed to rashness." The subject is considered under several headings.

Place of Established Operations in the Treatment of Cancer

An increasing awareness of the inadequacy of surgery in the treatment of cancer has led to much criticism and revision of established operations.* There are those who would replace radical subtotal gastrectomy with total gastrectomy for carcinoma of the stomach.[40-42] Others would revise the Miles operation to include a pelvic-lymph-node dissection, ligation of the inferior mesenteric artery at its origin and removal of the entire descending colon.[43, 44] The Halsted operation for cancer of the breast is being extended to include dissection of the supraclavicular and mediastinal lymph nodes with removal of a portion of the chest wall.[45,46] Hindquarter and forequarter amputations have been advocated for the treatment of malignant melanoma of the extremities.[47,48]

There has been a tendency to misinterpret many of these recommendations as an advocation of wholesale adoption of superradical operations. A careful study of the original contributions indicates that this is not the intent of the authors. Most of these are carefully controlled studies of what may be accomplished by widening the scope of the established operations. Excellent presentations of the temperate view of the more radical operations in the treatment of cancer have been made by Allen,[49] Gatch,[50] Carey and Kirklin,[51] Lahey and Marshall[52] and Baker.[53]

To date there is no evidence to justify any general or routine extension of the established operations for cancer. A judicious widening of the scope of the resection in particular cases is fully warranted, but before the superradical operations can be expected to replace the established ones, it must be shown that they can be performed with a reasonably comparable mortality and morbidity, and whatever disadvantages they may have in this or other respects must be compensated for by a distinctly superior cure rate. Not only will it take some years to establish this fact but also, if one considers the wide range in the biologic behavior of cancer, it appears quite unlikely that further extension of the areas of excision routinely applied will materially affect the over-all survival rate.

There are no natural boundaries to the growth of cancer. There is no reason to suppose that a tumor that has spread from the rectum to the hypogastric, iliac and the mesenteric lymph nodes will be miraculously blocked at the level of origin of the inferior mesenteric artery. Nor in cancer of the breast is it to be expected that a tumor that has spread to the axilla and the supraclavicular and mediastinal lymph nodes is not also extending into the opposite side of the chest and up and down the retropleural lymphatics. And these hypothetical situations take no cognizance of the frequent occurrence of direct spread of cancer through the blood stream, a circumstance that places the lesion beyond extirpation, however wide the regional excision.

It is abundantly clear either that the majority of tumors that respond well to surgical excision are confined to the organ of origin and the immediately adjacent tissues or that the metastases from such tumors are so constituted biologically that long periods of arrest of distant lesions follow removal of the primary growth. The consistently similar results of well performed surgery of the breast, stomach, colon and rectum over the years in the hands of different surgeons (for example, 7 to 10 per cent five-year survival in cancer of the stomach, 50 per cent survival in cancer of the breast and 45 per cent survival in cancer of the colon) suggest that this represents about the number of tumors biologically susceptible to surgical extirpation. It seems unlikely that superradical excision as a routine will materially affect these figures, but in the hands of all but the most gifted surgeons it will significantly increase the mortality and morbidity.

It is also clear that there can be no retreat from the established procedures. The hazard of cutting

*An established operation for cancer is defined as one that has been employed with only minor variations for many years so that the morbidity, mortality and percentage of arrested cases that follow its use are fairly well known. Examples are the Halsted operation for cancer of the breast, abdominoperineal resection for cancer of the rectum and radical subtotal resection for cancer of the stomach.

across a tumor in the process of its removal, the horrors of local recurrences in wounds and the empirical observations of all surgeons of experience that when one gets into tumor in the course of a dissection it is disseminated widely would render anything less than the established radical operations for cancer a regrettable backward step. Moreover, in certain areas there is an obvious need for certain revisions of the so-called "established procedures" in order that they may more adequately meet the demands of a good cancer operation, but without placing them in the superradical classification. An example is the emphasis that has been placed on the restriction of anterior resection of the rectum to tumors for which it provides a reasonably adequate margin of excision.[54-57] Another is the abandonment of "resection of the sigmoid" in favor of anterior resection or total resection of the descending colon for lesions involving the sigmoid.[58,59] The emphasis that has been placed on wider margins in cancer of the gastrointestinal tract in general and a trend toward combined oral and neck dissection for cancer of the oral cavity[59-62] are similar examples of the manner in which a careful review of the established procedures has led to a modification that improves its application but does not place it in the superradical category. The objective of a good cancer operation is a generous en bloc excision of all tumor without significant permanent disturbances of the patient's physiology or well-being and with little or no risk to his life.

Radical and Superradical Surgery

The opinion expressed in the previous section that superradical operations will not replace the established procedures as a routine does not imply that there is no place for the more extensive resections. Total gastrectomy with resection of the pancreas, spleen, colon, adjacent liver and all intervening lymphatic tissues is an acceptable operation for a huge, invasive, apparently slowly growing carcinoma of the stomach that has invaded locally without distant spread. This procedure, however, as a routine for cancer of the stomach is unthinkable, but where to draw the line between it and a wide resection of the stomach with removal of the omentum and ligation of the left gastric artery at its origin is a matter that must be decided in the individual case. Total gastrectomy for all operable gastric carcinomas is not a satisfactory compromise. There are many objections to it. First of all it is evident that it is not always necessary. Secondly, it unquestionably is a more disabling procedure to the patient than a radical subtotal gastrectomy. Thirdly, it is not a good palliative operation, being particularly badly tolerated by older patients with recurrent disease. In the over-all picture it will increase the morbidity and mortality of gastric surgery for cancer, neither of which can be overlooked. Finally, it will not solve the problem of the very poor results in gastric carcinoma. It adds to the total survival period chiefly when it is used for a slowly growing biologically favorable tumor that cannot be encompassed by subtotal gastrectomy. The incidence of such cases is low, but they constitute a brilliant example of the proper application of the more radical operations.[63]

The gross characteristics of an abdominal cancer are a most important determining factor in electing a superradical operation and are a better index to the biology of the lesion than the histologic appearances are. Any tumor that is large and locally invasive but in which there are no demonstrable lymph-node or distant metastases should be regarded as biologically favorable for surgical resection. No matter how large or apparently fixed such a tumor is, a superradical attack is justified. Some of the most gratifying of all long-term arrests follow such operations. On the other hand, diffuse peritoneal seeding in cancer of the stomach or the bowel, although it does not contraindicate a palliative removal of the primary growth, makes a superradical resection preposterous. The presence of liver or other distant metastases has a deterring effect upon the extent of an operation. How far one should go in the presence of such metastases must again be settled by the particular circumstances. In general, primary growths should always be removed. In abdominal lesions, solitary hepatic metastases involving the left lobe of the liver present a challenge that at times must be accepted. Involvement of the liver by direct extension, all other circumstances being favorable, requires excision.

These general principles are applicable to all cancers in all areas of the body. For example, resection of the chest wall for a neglected, slowly growing carcinoma of the breast is fully justified, whereas removal of the chest wall and dissection of the adjacent mediastinal lymph nodes for a small anaplastic carcinoma of the breast in a young pregnant woman with axillary and supraclavicular metastases obviously would be wrong. Between these extremes there can be no rules except the best judgment of the surgeon tempered by his appraisal of the probable biology of the tumor in question.

Carefully and judiciously applied, the superradical operations will contribute in a significant way to an improvement in the over-all survival rate of cancer. The surgical extirpation of huge tumors, biologically favorable but technically difficult, is the precise point at which a widening of surgical excision is indicated. A classic example is the experience with cancer of the upper third of the stomach. Here is a lesion that in the past has been turned down as "inoperable." In many cases, however, it was not associated with widespread metastases and with further improvement in surgical technics, the

routine radical resection of such lesions produced a significant improvement in the five-year survival rate.

One of the most pressing problems today is the place of pelvic exenteration for cancer of the uterus, cervix or rectum or for extensive irradiation necrosis. The results of Brunschwig,[64] Parsons and Bell,[65] Bricker and Modlin[66] and others[67] indicate that this procedure is already an established operation with an acceptable mortality and morbidity provided it is properly applied. Undertaken as a surgical feat for a biologically unfavorable tumor, it has nothing to recommend it. The future of the operation should be a restricted one since it is to be hoped that more and more surgically favorable lesions will be dealt with early and the surgically unfavorable lesions are not going to be significantly benefited by superradical surgery anyway. The application of this and all other superradical procedures for extensive cancer might be more judiciously applied if the operating surgeon were required to follow all these patients personally regardless of the outcome. A significant share of the emotional and economic burden that such operations produce would have a most salutary influence.

The expressed objection to superradical operations as routine procedures for cancer should not be construed as a criticism of surgeons who have undertaken a carefully controlled study of the results that can be obtained from a routine widening of the scope of the established operations. Such experimental departures are fully warranted, but advocation of general adoption of the procedures as a routine is illogical and certainly is not supported by any available data. If one considers the complex biologic nature of cancer, it seems clear that the place of the superradical resections must be a restricted one. Carefully applied to certain extensive tumors that are biologically susceptible to surgery, these procedures will have a permanent place in the surgeon's armamentarium.

Management of Recurrent or Metastatic Cancer

Despite a general swing toward surgical radicalism in the management of primary cancer, there is a persistent and not entirely warranted pessimism concerning recurrent or metastatic cancer. If one considers the complex behavior of cancer, recurrent and metastatic lesions occasionally must be amenable to surgical ablation. In some cases local recurrences are attributed to seeding of tumor at the time of a primary resection. The hazards of implantation of tumor cells during open anastomosis of the colon or stomach are greater now than the dangers of infection. Washing of the bowel with agents designed to inhibit implantation of cells at the suture line is becoming a common practice.[67,68,69] A study of the effects of the antibiotics on the transplantability of shed cells from lesions of the gastrointestinal tract is greatly needed. In other cases local recurrence may represent progressive carcinogenesis in a field of neoplasia rather than a disseminated lesion. In either of these situations reoperation is indicated, and long periods of arrest may follow such secondary operations.

The most aggressive attack on recurrent cancer has been advocated by Lewis and Wangensteen,[70] who advise taking a "second look" after an interval of two or three months in all cases of abdominal cancer with lymph-node metastases. The wisdom of this approach can be questioned. Recurrent tumor within a few weeks or months of a primary operation indicates either failure to extirpate a favorable lesion or very rapidly growing tumor in most cases. The fact that tumor has not recurred after a second look at intervals of three, six or even eighteen months does not ensure against a local recurrence. However, repeated surgical attacks on rapidly growing recurrent lesions may result in the salvage of some patients. The experience of Wangensteen and his associates suggests that this may be so, but more data are needed to decide when second and third operations are indicated.

Time is an important factor in assessing the biologic characteristics of a recurrent tumor. The longer the interval between the time of the operation and the appearance of a recurrence or metastases, the more favorable the secondary lesion is to surgical excision. In my experience, operations for recurrent cancer of the colon have produced long-term arrests only when the lesion recurred a year or more after the original operation.[71] Whenever a locally recurrent or metastatic lesion appears at an interval of a year or more after an initial operation and seems to be solitary and is so located that it can be resected, a secondary surgical attack is indicated. The initial characteristics of the tumor need not be considered when one is appraising the biology of the recurrence. I have seen recurrences successfully operated on when the initial gross and histologic characteristics of the tumor suggested that it was most unfavorable. For example, a moderately anaplastic tumor that had extended into the regional lymph nodes and had involved several adjacent organs was removed. A recurrence occurred eighteen months later and proved to be a mass of undifferentiated cancer cells, but after resection an interval of ten years has elapsed without recurrence. If the unfavorable pathological features of this tumor had been given undue weight, the opportunity to bring about a long-term arrest of cancer would have been lost.

Emphasis must be placed on the extraordinary behavior of metastatic cancer. The case reported by Trimble[72] in which the metastasis was excised three years before the primary tumor was removed is a case in point.

Long-Range Surgical Care of Cancer

The role of the surgeon in the palliative treatment of cancer is a most important one.[73] Because surgery still remains the only hope of permanent arrest of cancer, the surgeon stands in a position of singular significance to the patient. Whether he realizes it or not, he is the knight in shining armor who is going to save the patient from the cancer dragon. His lack of interest or his withdrawal from the case when it is evident to all that the battle is not won, takes all hope away from the patient.

The modern management of advanced cancer places a moral obligation on the surgeon to see his patient through one way or another. The daily care of the patient requires the services of an able and sympathetic physician or of an institution skilled in the management of these problems, but unless the surgeon is somewhere in the background, as the strategist if not the tactician, the patient loses faith and courage and his existence becomes a kaleidoscope of pain, despair and narcosis.

Most important of all, the surgeon is the only one equipped at the present time to evaluate the changing pattern of so-called "hopeless cancer." Once it is generally realized that a great many factors, most of them unknown at the moment, may influence the growth of cancer, a new vista full of hope is open to the patient with what is regarded as an incurable lesion. By taking full advantage of general supportive measures, by intelligent use of sedatives and narcotics, by judicious use of secondary operations, by irradiation both external and through radioactive isotopes, by appropriate administration of hormones and the antitumor drugs and by neurosurgical procedures for the relief of pain the surgeon may provide years of salvage from total disability; the progress attained is so encouraging that an aggressive confidence that something may be done must replace the archaic but still prevalent attitude of sympathetic despair commonly expressed to the patient's family in the words, "Too bad he didn't seek advice sooner; I can do nothing for him."

In this connection there is a need for much greater co-operation between radiologist and surgeon. The surgeon knows not only the patient but also the tumor. He has lived with the former, and he has seen, felt and generally appraised the latter. This background should be incorporated into the radiologist's phase of therapy in a way that no requisition blank can possibly fulfill. Radiation should be employed with the same accuracy and judgment as the scalpel. If there is reasonable expectation of destruction of the tumor, no holds are barred and a cancericidal dose should be given. On many occasions, however, the extent and nature of the lesion indicate that it is as far beyond radiologic arrest as it is beyond the reach of surgery, and under such circumstances the judicious application of radiation to symptomatic lesions may bring about extraordinary regressions without the severe disability that a cancericidal dose would occasion. Unconventional radiologic technics must have as important a place in the long-range control of "incurable cancer" as unorthodox operations on recurrent or metastatic lesions.

Secondary surgical attacks on recurrent or metastatic lesions are fully justified whenever a specific lesion in question is solitary, especially if it has developed at some time after the original operation. Excision of painful symptomatic lesions in the presence of other metastases is also advisable whenever this can be done without serious disability to the patient and with reasonable promise of a period of significant comfort and well-being. There is no substitute in this situation for the judgment that comes from experience in balancing the probabilities of cancer behavior.

Finally, when various chemotherapeutic measures are invoked, the management of the patient should not be dropped into the lap of the oncologist. It is essential that the care of the patient continue in the hands of a team composed of the surgeon, the radiologist, the oncologist and strong and sympathetic members of the patient's family.

A word of caution regarding palliative treatment and especially palliative surgery for cancer is necessary, however. The primary purpose of palliation is to relieve suffering, not to prolong the life of the patient. One of the greatest errors is to perform a colostomy for the pseudo-obstruction that commonly accompanies advanced abdominal carcinomatosis. Such a colostomy never functions properly, adds nothing to the patient's comfort, and greatly complicates his care. Another error is the "anticipatory colostomy" performed for "inoperable cancer" because the surgeon was sure obstruction would ensue. Anticipating the development of obstruction in gastrointestinal cancer is as unreliable and unwise as predicting the duration of life in all forms of advanced cancer. The surgeon must meet these exigencies as they arise, and the final decision whether or not to employ a palliative procedure must be determined by the probability of alleviating suffering, not merely of prolonging existence.

There is much muddled thinking in this regard, and too often the conscientious but misguided surgeon performs a colostomy or a gastrostomy and gives thousands of cubic centimeters of blood to drag out a patient's tortured existence for a few odd days or weeks. The surgeon has no right to take the patient's life, but he is likewise under no obligation to employ fantastic measures to prolong it in the face of intolerable and clearly terminal disease.[74, 75] Under these circumstances all measures should be designed to keep the patient comfortable, to help him face his dis-

ease and its probable consequences with courage and equanimity and to support his family, for whom the crisis, if it is well handled, is often more trying than for the patient himself.

In these terminal stages of cancer it is a great boon to all if both patient and all members of the family are fully aware of the nature of the disease. This is no time to dissemble. Patients are rarely afraid to die. They are always afraid if they are being deceived and seem to be abandoned. A good physician, a sympathetic surgeon clearly visible in the background, a united family, an attitude of aggressive optimism and a determination to control pain intelligently can make these tribulations not only bearable but deeply moving and ennobling experiences.

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MEDICAL INTELLIGENCE

PHEOCHROMOCYTOMA OF THE URINARY BLADDER*

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A PHEOCHROMOCYTOMA of the urinary bladder, to our knowledge, has not previously been reported. The discovery of this tumor in the bladder is of interest not only as a medical curiosity but also as an observation of general academic as well as clinical significance, for the finding is evidence that chromaffin tissue can occur in that organ.

CASE REPORT

A 74-year-old woman entered the hospital on March 24, 1950, because on two occasions she had noticed blood in the urine unaccompanied by pain. Except for measles 15 years previously, she had always been well.

The past history disclosed no complaints except the painless hematuria.

On physical examination the salient finding was a blood pressure of 220/110. The pulse was, however, regular in rate and rhythm. Blood studies were evaluated as within normal limits. The urine revealed numerous blood cells but was otherwise normal. Intravenous urograms delineated a normal upper urinary tract. The shadow of the bladder appeared normal in contour and smooth in outline. No filling defect was visible. On cystoscopic examination, however, a mass about the size of a small plum was discovered attached to the dome of the bladder by a broad pedicle. Its smooth, bluish surface was interrupted by a small, irregular ulceration of the dependent face, the probable source of the bleeding. Since the nature of the tumor was not recognized and the risk of transurethral removal of tissue in this case was equally unknown, biopsy was omitted.

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Under spinal anesthesia, the dome of the bladder was exposed retroperitoneally but was not immediately opened. Uninvolved bladder, well away from and around the periphery of the tumor, was grasped with Allis forceps and the entire segment excised with the tumor. In this manner the tumor was removed without having been manipulated or otherwise traumatized and with a good margin of grossly normal vesical tissue. It was assumed for general surgical purposes that a malignant tumor was being removed. As it happened, it was perhaps fortunate that the tumor, which proved to be epinephrine producing, was respected. During the operation, the blood pressure fell from 200/110 to 120/60. Postoperatively it rose gradually to 178/82. Repeated blood-pressure readings up to January 30, 1953, did not vary significantly from 170/88. Cystoscopic examinations after the operation gave no evidence of recurrence. No pressor tests were performed.

On the 1st postoperative follow-up visit, additional historical data were elicited. For three years before operation, the patient had experienced attacks of tachycardia and flushing of the face. At these times her neck became red, and her heart felt as if "water was running out of a bottle." Sometimes there was an associated prickling sensation down the arms that lasted only a few minutes. More than once a day for at least 2 years the heart beat rapidly after she emptied the bladder; she later modified her statement to the effect that the heart beat rapidly after every emptying of the bladder and during the night when the bladder was full. After the operation all these symptoms disappeared completely, and she wondered if the disappearance of the symptoms was in any way related to the recent operation. Up to the present the symptoms have not recurred.

Examination of the gross specimen revealed a firm, resilient, ovoid tumor measuring 4 by 3.8 by 3 cm. It was sessile. The amputated base measured 2.5 cm. in diameter and was surrounded by a narrow margin of bladder wall. The mucosa of the bladder was reflected over the surface of the tumor. It was reddish brown, mottled and smooth except over the dome of the tumor, where it was finely granular. There was a small, sessile, secondary nodule protruding from the surface of the dome of the mass. This nodule measured 5 mm. in diameter. The cut surface of the tumor showed the central portion to be hemorrhagic and necrotic, with areas of liquefaction. There was an irregular, broad rim of mottled, pinkish-white, soft, fleshy tissue deep in the capsule; the capsule was poorly defined and thin and appeared to consist largely of the covering mucosa of the bladder, which was deficient over the dome of the tumor and the protruding nodule. The base of the tumor was well demarcated from the underlying wall of the bladder. The cut surface of the tumor after fixation in formalin showed mosaic gray-brown to pale-brown mottling.

Histologic examination¶ was reported as follows:

> This is an unusual tumor in an equally unusual location. It is very cellular, and its stroma is represented by a rich but inconspicuous and delicate network of capillaries (Fig. 1). The cells are closely packed to form solid sheets of varying size, interrupted here and there by large vessels bordered by a minimum amount of connective tissue and by bundles of smooth-muscle fibers—remnants of the muscular wall of the bladder. The cells build no fixed pattern, and one field looks much like another. There are two patterns, however, that recur from time to time throughout the growth. One of these is characterized by an orderly radiation of cells about a capillary that, when seen in cross section, resembles a rosette; the other resembles a feather with a uniform, single layer of cells

¶Sacred Heart Hospital S-50-233.

running out along both sides of a capillary. This close association of tumor cell and capillary is a conspicuous feature of the tumor. At the periphery, the outer margin is well defined, though there is no capsule.

Invasion is an obvious feature of this tumor, for it occupies the entire thickness of the bladder wall. It reaches to and penetrates the mucosa. The tumor replaces the submucosa, muscularis and adventitia of the bladder. Remnants of muscularis, appearing as bundles of smooth-muscle fibers, are scattered throughout the tumor.

The tumor is made up of one class of cells. These are large—many times larger than histiocytes. The majority are fairly uniform and yet they vary, and small and large cells may be found in any field. There are no demonstrable cell membranes and because the cells are closely packed, the

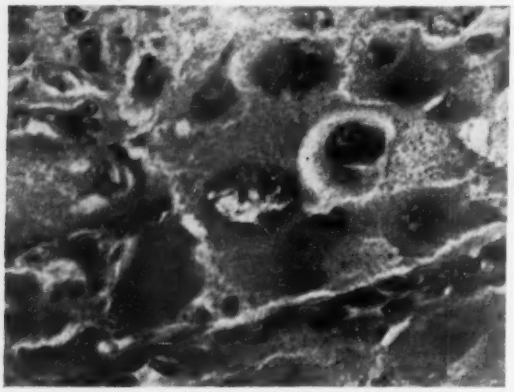

FIGURE 1. *Photomicrograph of the Specimen (X400), Showing a Small Field Comprising Several Tumor Cells Intimately Associated with a Capillary Network (Note Particularly the Variability in Size of the Cells and Nuclei, the Absence of Cell Membranes and the Basophilic Granularity of the Cytoplasm).*

cytoplasm of one often merges imperceptibly with that of another. Each cell has a relative abundance of cytoplasm. This is homogeneous and finely granular; these granules are distinctly basophilic. *This fine, basophilic granularity of the cytoplasm is the most distinctive characteristic of the tumor.* The cytoplasm of some of the cells also contains a fine, brown pigment that varies in amount, in concentration and in distribution within the cell. This pigment does not stain for iron, and its physical characteristics resemble those of melanin. Occasionally, the cytoplasm is vacuolated or contains eosinophilic hyaline inclusions of varying shape and size, but such cells are not common. To describe the shape of the cells "pleomorphism" seems the best term.

The nuclei are quite as variable in size and shape as the cells are. The nucleus-cytoplasmic ratio strongly favors the cytoplasm. The position of the nucleus varies, but it usually lies near the periphery. Each nucleus has a sharply defined, though often crenated, nuclear membrane, possesses one or two large nucleoli and a fairly granular nucleoplasm. Double and multiple nuclei are common. Some are very hyperchromatic, but, and this seems important, mitoses are conspicuously absent.

The diagnosis is bladder wall showing a locally invasive tumor having the histologic characteristics of a pheochromocytoma.

DISCUSSION

The peculiar character of the pheochromocytoma cell, its manner of growth and its relation to capillaries are features that resemble most closely the histology of the adrenal medulla. Its obvious capacity to invade justifies its classification as a malignant tumor, and yet the absence of mitoses and lack of cellular dissociation suggest a relatively benign lesion. Tumors of this type are usually found in the adrenal medulla but apparently may arise wherever this particular type of paraganglionic tissue is found, and from our own studies such a location is the adventitia and wall of the bladder. It seems reasonable to assume that the tumor originated from this location in the case reported above.

SUMMARY

What appears to be the first case of pheochromocytoma of the urinary bladder is reported in an elderly woman. The mucosa of the bladder was invaded by tumor tissue, leading to hematuria. The history before and after operation strongly suggests that this was a functioning tumor. The probable origin of the tumor in paraganglionic tissue situated in the wall of the bladder is supported by the observation of such tissue in this location in normal bladders.

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DOCTORS AFIELD

John Keats, 1795–1821

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IN his youthful behavior John Keats conformed to the average with a preference for physical rather than mental activities. He loved the fields and streams and often came home with prized zoologic specimens. His education was pursued under sharp financial restrictions, but by the time his school days were over, he had acquired a rare knowledge of nature, a pure sense of beauty and a creative penchant that gathered poetry as a bee gathers honey. While he was still a youth his acute awareness of the earth's silent phenomena made it possible for him to write:

> . . . and then there crept
> A little noiseless noise among the leaves
> Born of the very sigh that silence heaves.

When he was fifteen years of age his mother died of consumption. The time spent at her bedside and the sight of her slow surrender added to the psychologic wrench of his father's death. Not only did he inherit his mother's physical features, but also his nervous instability, his personal charm and his poetic urge were obviously of maternal origin. No doubt before her death his destiny was sealed by a massive dose of her own tubercle bacilli.

Through these catastrophic strokes the young Keats was swiftly swept toward mental maturity.

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He ceased to vacillate between pleasure and duty and delved deep into literature, burying his sorrow in hard work and finding recompense in books. During his last years in school he won all available prizes and honors.

His guardian, an obdurate businessman, decided that John Keats should study medicine. As far as the record goes, he accepted the score with no objections and made good in spite of the fact that he was temperamentally unfitted for the task.

According to custom he was apprenticed to a surgeon for a period of five years. He lived with his preceptor, Thomas Hammond, at No. 7 Church Street, only a few steps from Lamb's Cottage. There is nothing to indicate that he came under the spell of his neighbor, but it is known that he was only a two-mile pleasant walk through friendly fields from his friend and former teacher, Cowden Clarke. While thus afield he indulged in poetic musing, and upon arrival at the school he enjoyed literary discussions and departed with borrowed books under his arms and abiding satisfactions in his heart. Fortunately, Hammond had two apprentices, making it possible for Keats to enjoy these literary interludes.

Suggestive of his capacity for work stands the fact that in spite of his poetic diversions he entered the second phase of his medical education at the end of four years instead of five. White[1] said, "For some unknown reason his apprenticeship was shortened to four years," and he entered the medical school at Guy's Hospital on October 1, 1815. At the Hospital there are three books in which his name was inscribed. An autograph thief clipped his signature from the one signed by new students. But his name remains in the book of entry for Physicians' and Surgeons' Pupils and Dressers, and in the third book, entitled, "Surgeons' Pupils of Guy's and St. Thomas's Hospitals." White's[1] interesting story of this period indicates that Keats accepted the harness of the medical student and performed well in all classes. He entertained a natural repugnance to the premature resurrections in London churchyards, occasioned by the clever rascals known as body snatchers. He abhorred the foul-smelling wounds reeking with "laudible" pus as he made daily rounds with his plaister box and only "handywomen" to help with his dressings (this was before the days of Lord Lister and Florence Nightingale). Likewise, it should be said that the stifling atmosphere of the operating rooms and the cruel cutting without anesthesia were wholly incompatible with his sensitive soul.

But on the whole these exacting experiences did not materially interfere with his creative bent. Apparently, he developed the incredible capacity of scribbling poetry on nondescript scraps of paper or the margins of his notebooks without altering the character or continuity of his medical notes. In a letter to Cowden Clarke the following example occurs: "The other day during the lecture there came a sunbeam into the room and with it a whole troop of creatures floating in a ray; and I was off with them to Oberon and fairyland." Also he found time to draw pictures of flowers and fruit while he was attending lectures.[2]

Yet he was keenly alert to the medical problems of his day and their implications. There is evidence that Keats diagnosed the doctor as well as the patient. On one occasion he said, "Medical men guess; if they cannot ascertain a disease they call it nervous." There are other passages indicating a rare perspicacity in connection with his brief medical career. His intimate friend and biographer, Charles Armitage Brown,[3] considered him indefatigable in his medical studies. James Curry, one of the physicians to Guy's Hospital, referred to Keats' acuteness of mind, brilliancy of talent and truthfulness of observation.

On July 25, 1816, Keats presented a testimonial from Mr. Hammond and passed his examination before the Apothecaries Society in London. Possibly, he had to wait until the end of October before receiving his diploma since the regulations required that the candidate should be twenty-one. In St. Thomas Street with his fellow lodgers, his inspiration point was the window seat familiarly known as Keats' seat, from which his creative spirit launched its poetic flights. In one of these flights he said to his friend, Stephens, "A thing of beauty is a constant joy." Stephens thought it wanted something. Then with the glow of creative accomplishment Keats exclaimed, "A thing of beauty is a joy forever." Thus, young Keats was ever straying from strict medical duty to the pleasurable path of poetic beauty. Finney[4] states that before his examination by the Apothecaries Society the chronology of his poems contained 26 entries. Within two months of his examination he had written "O Solitude" and "To One Who Has Been Long in City Pent." Shortly before, according to John Middleton Murry,[5] he had penned "perhaps the finest sonnet in our language entitled 'On First Looking Into Chapman's Homer.'"

All this belies Keats' apparent intention of following the profession of medicine. Yet the ease with which he negotiated his examinations and the establishment of Keats' Ward at Guy's Hospital testifies to his presence in the Hospital and the character of his work as a student of medicine. In August, 1816, he wrote a long letter to his brother, George, in which he expressed a longing for poetic accomplishment with never a word about medicine. His friend Brown[3] indicates that early in 1817 Keats had decided not to practice medicine. Before this he had said, "My last operation was the opening of a man's temporal artery. I did it with the utmost nicety, but reflecting on what passed through my mind at the time, my dexterity seemed a miracle, and I never took up the lancet again." Apparently

without regrets he gave up medicine in favor of poetry, but he calculated that his knowledge of medicine contributed "toward the great whole."

His brother, Tom, was dying of tuberculosis when Keats traveled to Liverpool to see their brother, George, and his bride off to America. On this excursion he visited his old friend Stephens, who was practicing surgery in the country town of Redbourne, and Keats informed him that poetry was in command and that he had definitely abandoned medicine.

Soon after this his brother, Tom, died. Keats had spent days and nights at his bedside, and on February 3, 1820, he suffered severe bleeding from his own lungs. To the modern student of tuberculosis this was not the first manifestation of the disease, but to Keats' physicians even pulmonary hemorrhage was not of diagnostic significance. They thought the disease was in his mind — not in his lungs. Apparently, they spurned Auenbrugger. They failed to listen to their contemporary,Laënnec; they had no thermometer with which to measure temperature. There was no way to examine the sputum. There was no roentgen ray to extend their vision; consequently they did everything they should not have done, including the repeated letting of blood from veins already depleted. Only recurrent hemorrhages, progressive physical depletion and the surprising findings at autopsy revealed their professional shortcomings.

But Keats was not deceived. With remarkable discernment he said, "I know the colour of that blood; it is arterial . . . that drop of blood is my death-warrant." This first frank hemorrhage was a major disturbing factor in his life, augmenting his literary misgivings, accenting his financial anxieties, reactivating his conflict with his guardian, heightening his passion for Fanny Brawne, and making more evident his uncertain future, with revival of the question whether he should or should not practice surgery.

The story of this mental struggle while his body was being consumed by tuberculosis is of great medical interest. His hopeless journey to Italy and his rapid decline and death in the Piazza de Spagna in Rome, with his faithful friend, Severn, and the kindly Dr. James Clark (later Sir James), in voluntary attendance, are of further medical interest since Sir Luke Fildes' well known painting "The Doctor," recently widely publicized, is supposed to represent the sympathetic features of the compassionate Sir James.

Fondling an oval carnelian, the gift of Fanny Brawne, as the end drew near, Keats instructed Severn to put her letters next to his lifeless heart before burial in the English cemetery near the Pyramid of Caius Cestius, with violets overflowing it. Severn said that Keats occasionally sent him to see this lonely, but lovely, spot so that he could describe it to him. This is easier to understand when one recalls that Shelley once said: "It might make one in love with death, to think that one should be buried in so sweet a place."

On February 23, 1821, the pathetic life of John Keats came to a peaceful end, so quiet that his faithful friend Severn "still thought he slept."

His burial was equally quiet, but before Shelley's own ashes were deposited near Keats' dead body in his "Adonais" he paid due homage to this lamented young physician so far afield.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 39271

PRESENTATION OF CASE

A fifty-seven-year-old Greek-born cobbler entered the hospital with the diagnosis of rectal polyps.

About a year before entry he first noted bleeding by rectum with each bowel movement. For years he had been constipated and had treated himself with cathartics and oil enemas. Three months before admission a proctoscopic examination had demonstrated fresh blood coming down from above the rectosigmoid. A barium-enema examination at this time and another two days before entry demonstrated two polyps at the apex of the sigmoid loop. There was no history of weight loss or change in bowel habits.

The past history and review of the systems were noncontributory.

Physical examination showed a well developed and muscular man. The head and neck were normal. The heart was not enlarged; the rhythm was regular, and no murmurs were heard. There were a few dry expiratory rales in both lungs. The abdomen was normal except for small bilateral inguinal hernias. Rectal examination was negative.

The temperature, pulse and respirations were normal. The blood pressure was 170 systolic, 85 diastolic.

Examination of the urine was negative. The blood hemoglobin was 14.2 gm. per 100 cc., and the white-cell count 8700, with a normal differential and smear. The prothrombin time was 15 seconds (normal, 14 seconds). The nonprotein nitrogen was 24 mg. per 100 cc. A blood Hinton test was negative.

In the hospital the patient received sulfathalidine, 2 gm. by mouth four times a day for the four days before operation, and streptomycin, 0.5 gm. by mouth twice a day for the two days just before operation. On the fifth day an uneventful sleeve resection of the polyp-containing length of sigmoid was carried out, during which he received 500 cc. of whole blood. Postoperatively, he received streptomycin, 0.25 gm., and penicillin, 100,000 units intramuscularly, every six hours. The postoperative course was unremarkable for the first thirty-six hours. The Levin tube was removed at the end of the first postoperative day. Peristalsis was normal; the abdomen was flat and soft; the chest was clear; and the patient was taking fluids by mouth. On the evening of the second day the temperature rose to 103°F. The patient vomited and had several loose stools. He complained of general malaise but had no specific pains or complaints. The abdomen was soft and nontender. On the third postoperative day the white-cell count was 4600. The urine was cloudy and gave an olive-green reaction for sugar, and a ++ test for albumin and bile. The sediment contained many bacteria, 40 to 50 red cells and 10 to 15 white cells per high-power field. During the third day the patient became increasingly ill. The temperature rose to 104.8°F., the abdomen became distended, and he became confused. Diarrhea persisted though diminishing. Peristalsis was present, and there was no abdominal tenderness, guarding or spasm. The lungs became filled with coarse rales, and he began coughing up thick, brown sputum, but an x-ray film of the chest showed that the lungs were clear. There was no costovertebral-angle or calf tenderness. A Miller–Abbott tube was passed. On this day the patient received 1500 cc. of 5 per cent dextrose and water and 2000 cc. of 5 per cent dextrose and saline solution, having up to this time received 1500 cc. of 5 per cent dextrose and water and 1000 cc. of dextrose and saline solution a day since operation. On the morning of the fourth day he was found in shock, with mottled cyanosis and a blood pressure of 64 systolic, 40 diastolic, a temperature of 105°F., a pulse of 120, and respirations of 35 to 40 per minute. Respirations were labored, but the lungs were clear. The abdomen was soft and slightly distended, with some guarding in the left lower quadrant. There was a slight subcutaneous emphysema along the left side of the abdomen extending into the left axilla. The operative incision appeared healthy. Rectal examination was negative. Only 10 cc. of urine had been passed since midnight. The white-cell count was 16,000.

A Levin tube was inserted to replace the Miller–Abbott tube, which the patient had pulled out several times. He was given a transfusion, and a second operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. OLIVER COPE*: The evidence indicates that this patient had the not uncommon condition of polyps in the sigmoid; he was given the usual preoperative preparation for resection of such polyps — that is, sulfathalidine for four days, six doses of 2 gm. each, and streptomycin added for the two days before operation. The operation apparently went uneventfully; there was nothing to tell us before

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or during operation that anything unusual was to be anticipated. After operation he again received chemotherapy; the dosages were changed and it was given intramuscularly instead of into the bowel. The dosage of streptomycin was reduced to 1 gm. a day, and the penicillin was a moderate, almost a modest, dose of 400,000 units a day. One might wonder whether that dosage of chemotherapy postoperatively was enough to handle a massive infection. I assume that it was not, because the subsequent history was that of a severe, overwhelming infection.

First of all, the patient did not seem to suffer primarily of intestinal obstruction. I shall dismiss the small hernias that were noted before operation; there apparently was no secondary intestinal obstruction from an incarcerated hernia or an obstruction at the site of the intestinal anastomosis. The predominant symptom was initially diarrhea, with mounting signs of infection. In view of the chemotherapy given preoperatively to the bowel the first condition one thinks of is a rare complication, an overwhelming staphylococcal infection developing in the intestinal tract. This staphylococcus would have been an organism that grew independently of the chemotherapy while the other organisms were suppressed, leading to a selective infection. The staphylococcus is the organism most often reported. Theoretically, others would survive the chemotherapy and infect similarly.

Was this a staphylococcal infection? The diarrhea was early and prompt but not persistent. Apparently, it was diminishing; therefore, I would say that the primary infective process was not within the large bowel — that is, it was not a suppurative mucosal diarrhea. Then there was the development of pulmonary edema and the raising of thick, brown sputum without x-ray evidence of infarction or pneumonia. Is it true that the x-ray picture was negative?

Dr. Joseph Hanelin: I think it was.

Dr. Cope: That is extremely important. A staphylococcal septicemia produces multiple small septic infarcts in the lung, but I do not know if this pulmonary picture could have been caused by the staphylococcus. The classic organism producing this pulmonary edema and hemolysis is one of the clostridia group, principally the histolytica. During World War II Krayer et al.[1] investigated the experimental relation of the clostridia organisms to toxic shock. They showed that certain toxins of the clostridia group, principally that of the histolytica organism, when diffused through a heart-lung preparation gave no effect for a period of four hours; then, quite suddenly, massive pulmonary edema appeared. This time relation of pulmonary edema in the experimental setup was comparable to that seen in the intact animal — that is, there is a latent period for toxin action, and then severe pulmonary damage occurs. These toxins also produce hemolysis so that an interpretation of what is described as having occurred in the pulmonary tree of the patient under discussion is a circulating toxin of the type produced by the clostridium organism, causing hemolysis and pulmonary edema. Is the x-ray picture consistent with pulmonary edema?

Dr. Hanelin: No; not on the day before the second operation.

Dr. Cope: Other organisms such as streptococci and staphylococci produce hemolysis. I was trying to tie all the manifestations together. So much for the lung picture.

The subcutaneous emphysema that was noted running up the left side of the abdomen from the region of the incision toward the axilla indicates a gas-producing infection traveling along the lymphatic pathways to the axillary lymph nodes. Clostridia can do this but so can some of the streptococci. I do not recall ever having seen emphysema from a staphylococcus. Taking hemolysis, pulmonary edema and subcutaneous emphysema together, I am forced to the conclusion that I am not dealing with a staphylococcal but with a clostridial or streptococcal infection. Since the streptococcus should be the organism most easily eliminated by the chemotherapy, I am left with the impression that the infection was due to a clostridium.

How could a clostridium have produced the infection? Clostridia are normal inhabitants of the lower intestinal tract and may not have been eliminated by preoperative chemotherapy. At operation it is almost impossible to do an intestinal anastomosis without some degree of contamination; therefore, it is reasonable to expect that this organism was present in the patient under discussion. Why they gave rise to such a fulminating type of infection I do not know. Ordinarily they flourish in necrotic tissue, under conditions of anoxia — that is, tissue devoid of blood supply. It is rare for such a virulent infection to follow an anastomosis of the bowel with its mesentery intact. Could there have been some anomaly of the arterial supply to the loop of sigmoid that was resected? Such a condition must be extremely rare, and it is difficult to incriminate the intestinal anastomosis.

I summarize by saying that this patient had overwhelming infection, probably not by the staphylococcus, more likely by the intestinal streptococcus or the clostridium. The last is the most likely. Presumably, there was some condition producing anoxia in the region of the intestinal anastomosis. The second operation was done to recognize and eliminate the necrotic tissue. The patient seems to have been very ill. I am amazed that he was taken to the operation with as little as one blood transfusion.

Dr. Robert S. Shaw: The degree of emphysema of the abdomen was less than is apparent from

the transcript. It was noted by one observer, who, as I recall, was most impressed with it in the left lower quadrant adjacent to the wound. I was unable to elicit it two days later.

DR. COPE: That diminishes the likelihood of a clostridial organism but does not eliminate it. What one needs are cultures; for example, I have been forced to dismiss all the bacteria in the urine. What were they? That might have offered a lead. The urinary findings were consistent with a severe, overwhelming infection. I suppose blood cultures were taken. I should have expected that they were positive. Obviously, if the report had given a positive finding, it would not be a problem.

DR. JOHN B. STANBURY: What does Dr. Cope consider the main area of infection — in the anastomosis or in the peritoneal cavity?

DR. COPE: It would be hard from any evidence I am given to fix it anywhere but around the wound; since the incision was described as being clean, the sepsis was deep, presumably inside the peritoneal cavity.

CLINICAL DIAGNOSES

Sigmoid resection for polyps.
Peritonitis, acute, ?anastomotic leakage.

DR. OLIVER COPE'S DIAGNOSIS

Peritonitis and septicemia, with primary infection in region of anastomosis, ?clostridial, ?streptococcal.

ANATOMICAL DIAGNOSES

Staphylococcal membranous enteritis.
Septicemia, staphylococcal.
Bronchopneumonia, with abscess formation.
Operation: sigmoid resection for polyps.

PATHOLOGICAL DISCUSSION

DR. GEORGE S. SPEARE: We were thinking along the same lines that Dr. Cope did; we thought of staphylococcal infection and took a stool culture. On the fourth day the diarrhea started; the white-cell count went up; the abdomen became more distended with some tenderness and was silent; the amount of emphysema really was not impressive. We believed some infection in the anastomosis was producing increasing peritonitis. Dr. Bartlett and I spent four or five hours on the fourth day trying to rule out trouble in the anastomosis and decided to do a transverse colostomy under local anesthesia. We found clear fluid, and acutely inflamed edematous small bowel with injected blood vessels. The colon was not as markedly involved as the small bowel. We exteriorized a loop without opening it. Because the tenderness was in the region of the left lower quadrant, where the anastomosis was, we made a small McBurney incision with the idea of putting in a drain; we found clear fluid and no induration or mass around the region of the anastomosis. We closed this without drainage.

DR. BENJAMIN CASTLEMAN: The patient died two days later. At autopsy the anastomosis was intact, but the entire small bowel from the ligament of Treitz to the ileocecal valve was markedly inflamed, with little exudate over its surface. At the time of autopsy there was about 1500 cc. of slightly turbid fluid in the peritoneal cavity. When the bowel was opened most of the mucosa had been sloughed off, leaving a raw granular surface; lying on the mucosa, in some places free and in others adherent, was yellowish-gray membranous slough (Fig. 1). Some of these pieces of membrane formed casts and migrated down the bowel. A culture of the material in the small bowel as well as of the blood grew staphylococci, which apparently were not sensitive to penicillin, streptomycin and the various other antibiotics, including terramycin and aureomycin.

FIGURE 1. *Appearance of the Bowel at Autopsy.*
The small bowel on the left shows an adherent membranous slough on denuded granular mucosa. The right section shows a longitudinal cast on only partially involved mucosa.

Microscopically, there was little mucosa left and the inflammatory exudate was composed of mono-

cytes, phagocytes and lymphocytes, and very few polymorphonuclear leukocytes. A few epithelial cells were still present in the glands and there was an attempt at repair. The slough was composed of necrotic material, polymorphonuclear leukocytes and clusters of staphylococci.

Dr. Paine, would you comment about the bacteria?

Dr. Thomas F. Paine: When the antibiotics are given by mouth everyone knows that the flora of the gastrointestinal tract changes very quickly. The type of change depends upon the sort of antibiotic given, and no doubt, on many other variables. If I had to face a bowel resection today I think I should prefer to face it with the organisms I am ordinarily used to having in my bowel rather than having a new species selected out through no choice of mine. Staphylococcal enteritis is one of the complications of antibiotic therapy. Other organisms than staphylococci may be associated with diarrhea in conjunction with the use of antibiotics. Not having to do surgery myself, ordinarily, I am not faced with this need to try to protect the patient from incidental infection at the time of resection. If the surgeon has to have the peace of mind that attends administration of a "prophylactic" drug before such a resection he must face the hazard of some such complication as this. Certainly, it is infrequent. Staphylococcal enteritis associated with antibiotic therapy has been described by Dr. Finland, of the Boston City Hospital,[2] and by workers at the Mayo Clinic[3] and at the Deaconess Hospital.[4] It seems to be a real bacteriologic entity in terms of what happens to the patient — there is a terrific degree of necrosis of the mucosa of the bowel, with the clinical picture of severe shock and severe diarrhea. And the staphylococci are usually resistant to one or more of the antibiotics that are being given.

Dr. Castleman: I believe you have had some experience with this, Dr. Welch.

Dr. Claude E. Welch: Unfortunately, yes. Since we recently had several patients with severe pseudomembranous ulcerative enteritis, Dr. Glenn Behringer collected the cases that have been observed in this hospital in the last two or three years. He found 8, of which the case under discussion was the most recent. Three of these patients recovered, and the others died. It is difficult to find the common denominator in the whole group. Most of the cases have followed operations on the colon. Recently, they all have been due to staphylococci, but even this is not always necessary. Certainly, the incidence has been tremendously increased by the use of terramycin or aureomycin, although the disease has occurred in a number of patients who have been prepared for colon surgery by sulfathalidine, and occasionally it has been found without previous use of any antibiotic whatsoever, as pointed out in papers from the Mayo Clinic.[3] The clinical course in the case under discussion was typical of the disease as we have seen it. Certainly, if diarrhea develops in the immediate postoperative stage, this complication has to be considered very seriously. If the patient is already receiving antibiotics, they probably should be stopped and erythromycin administered. Unfortunately, by the time the bacteriologic reports are received on such patients, they are either dead or too sick to be helped. Consequently, we have been culturing the bowel at the time of the operation so that, if staphylococci are found, preventive treatment may be started at once. Another important question is the source of these bacteria. Probably most of them are already in the bowel. Some of these patients have them in their own throats. Perhaps the physicians give them some. One precaution that we can take and undoubtedly needs more investigation is the sterilization of all the materials that are now stuck into the nose or into the stomach with equanimity, such as Levin tubes, Miller–Abbott tubes and intratracheal tubes. It may be that we can make some headway by paying attention to these sources of cross infection.

Dr. Marshall K. Bartlett: I saw this patient with Dr. Speare and I should like to share the responsibility for the second operation, particularly since it did not contribute to the patient's well-being. On the fourth postoperative day, the man was critically ill with overwhelming infection; his abdomen was moderately distended and somewhat tender, particularly in the left lower quadrant, and completely silent. It seemed to us that in addition to the possibility of the enteritis there was the possibility of a generalized peritonitis. If so, and if it was due to leakage at the suture line, there was some chance that we could help by stopping the continuing contamination by means of a transverse colostomy. When the incision was made in the right upper quadrant, it was obvious that there was no generalized peritonitis, but the small bowel was inflamed and edematous as described by Dr. Speare. Consequently, because of the crepitus in the left lower quadrant, we also made a small left McBurney incision to be sure there was nothing in that area that could be benefited by drainage or some other surgical procedure and to rule out the possibility of necrosis of the anastomosis. The course from then on was steadily downhill in spite of all our efforts of replacement of blood, plasma, fluid and electrolytes. None of the bacteriology was available at the time the decisions were made. Stool culture had been taken, but could not be read that soon. We gave the patient aureomycin intravenously, which we now know was not an effective agent. Without any knowledge of the type of bacteria present we decided to use that as a broad-spectrum antibiotic.

DR. COPE: A very significant thing, of course, is, as Dr. Paine said, that this complication is an example of the back-firing of chemotherapy. It is frightening!

DR. WALTER BAUER: I wonder if Dr. Paine can say anything more about the original chemotherapy in this case or in a similar case in which one has to proceed without knowledge of the type of organisms present.

DR. PAINE: I think it is difficult to try to generalize about these points because the bacteria involved in "antibiotic enteritis" may not be staphylococci. When one is considering the patient perhaps it is a good idea not to generalize. Obviously, if the bacteria are not responding to the antibiotic being given, some other antibiotic should be used.

DR. REED HARWOOD: I should like to ask Dr. Paine if he has seen that sort of enteritis after the treatment of upper respiratory infections.

DR. PAINE: This is not a surgical complication; it is a biologic complication, and it can occur with the use of antibiotics for medical conditions. The cases at the Boston City Hospital that I know about were medical cases.

DR. CASTLEMAN: It should be mentioned that this condition was seen especially involving the colon rather than the small bowel before the days of antibiotics — perhaps not as often. This patient had a septicemia at the time of death and also a severe pneumonia with abscess formation so that the pneumonic complication was certainly an aggravating factor in his death.

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CASE 39272

PRESENTATION OF CASE

A seventy-five-year-old woman was brought to the Emergency Ward by ambulance because of severe chest pain and "collapse" of about five hours' duration.

The patient had felt unusually fatigued for the week before admission but attributed this to her being out of the house for about ten hours each day. On the morning of the day of admission while dressing, she was suddenly seized with a "violent ache" in the right cheek, which rapidly spread to the entire anterior part of the chest, causing her to feel extremely faint. This lasted about five minutes, during which she had the sensation of impending death. She did not recall any radiation of pain to the arms, shoulders or back. When the pain had passed, she collapsed on her bed, faint but not unconscious, and remained so until found by the chambermaid two hours later. Since the onset of pain she had had a "painful distaste" for food, with nausea, and vomited once. She had moderate periumbilical pain for a short while soon after the chest pain. No other symptoms were present before the onset of the acute episode. Bowel movements had been normal, without evidence of blood.

During the past three to five years she had occasionally awakened at night with severe, squeezing pain in the anterior portion of the chest, usually on the left, radiating to the left shoulder and arm, and lasting only a few minutes; she "thought it was neuritis." Sometimes she had to sit up in bed to relieve the pain. Occasionally, she had similar pains during the day that had recently become more frequent. She was last examined by a doctor eight years before admission, when the heart and blood pressure were said to be normal.

Physical examination showed the patient lying apathetically in bed. The skin was pale, cold and clammy, and the lips were slightly cyanotic. The pupils were equal and reacted to light, and on accommodation; the fundi showed only minimal tortuosity. The neck veins were distended but did not pulsate. In the chest, breath sounds were decreased, with slight dullness in the left base but no rales. The left border of the heart was not definite. Heart sounds were distant, and no murmurs were heard. The liver edge was sharp, firm and nontender and was palpable 3 fingerbreadths below the costal margin. The spleen was felt 2 fingerbreadths below the costal margin. The abdomen was somewhat distended and tympanitic, with good peristaltic sounds, and was not tender. There was no peripheral edema.

The temperature, pulse and respirations were normal. The blood pressure was 70 systolic; the diastolic pressure was unobtainable.

A urine specimen was insufficient for specific-gravity determination. It gave a +++ test for albumin but was otherwise normal. Examination of the blood revealed a hemoglobin of 14.0 gm. per 100 cc. and a white-cell count of 23,800, with 47 per cent neutrophils, 38 per cent monocytes, 6 per cent atypical lymphocytes and 9 per cent lymphocytes. An electrocardiogram was considered to be within normal limits. A roentgenogram of the chest revealed a dorsal kyphoscoliosis, enlargement of the heart in the region of the left ventricle, a tortuosity of the aorta and apparently some congestion of the pulmonary vessels (Fig. 1). There were densities in both upper lobes that were believed to be probably due to old tuberculosis. There was no recent consolidation.

The patient was put to bed in a shock position and given stimulants. She remained in shock dur-

ing the night, and the next morning was given Cedilanid and placed in an oxygen tent. A second electrocardiogram was consistent with digitalis effect. She remained hypotensive, became comatose

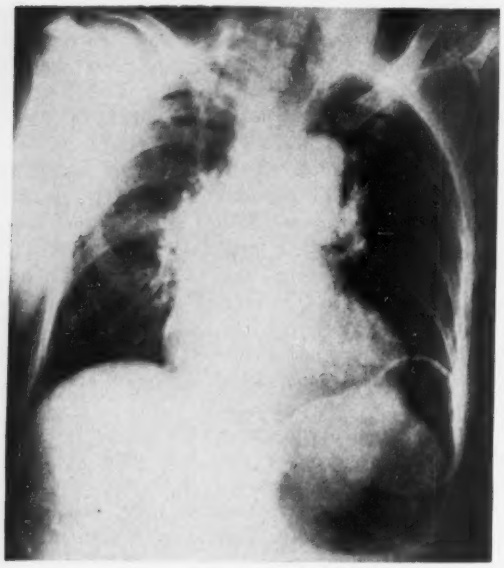

FIGURE 1.

and after vomiting up a small amount of brownish material died about seven hours later, twenty-seven hours after admission.

DIFFERENTIAL DIAGNOSIS

DR. ROBERT S. PALMER*: Statistically, this seventy-five-year-old woman had a 75 per cent chance of having hypertension. Patients with hypertension who have sudden severe chest pain are likely to have coronary thrombosis; if in addition there is diabetes, coronary thrombosis is even more likely. This patient had neither hypertension nor diabetes. Certainly, she did not have hypertension at the age of sixty-seven when last examined. The severe, squeezing pain in the anterior portion of the chest in the previous three to five years, usually on the left, radiating to the left shoulder and arm, suggests coronary insufficiency. That the pain awakened her at night may indicate that she had angina decubitus and therefore quite severe coronary-artery disease. The pain before the last acute illness may have been due to a hiatus hernia or some other condition, but I think it was coronary in origin. That sitting up relieved the discomfort is characteristic of hiatus hernia, congestive heart failure and coronary-artery disease. In this patient similar pains occurred during the day and increased in frequency, consistent with exertional angina. Coronary insufficiency or thrombosis may produce pain in the chest and, unaccountably, pain in the face. I think the shock, even with the normal electrocardiogram, on the whole favors coronary thrombosis. With coronary thrombosis severe enough to kill, however, I should expect acute changes in the electrocardiogram to have been apparent even in a matter of a few hours. Of course this patient, who had a large heart without hypertension, may have had chronic coronary insufficiency — that is, an old coronary closure. But the distribution and character of this new pain the day before death and especially the suddenness of its onset are against coronary thrombosis. It usually takes more time than in the present case for an acute coronary thrombosis to develop symptomatically.

On the basis of the last thirty-two hours of this patient's life, I believe everyone is thinking of dissecting aneurysm of the aorta just as I am. I know of a case in which dissection of the aorta extended upward to involve the great vessels and produced a sudden, brief, severe pain across the forehead as the only symptom. The next morning the patient was found dead in bed; the aneurysm had ruptured and caused death during the night. I bring up this case to demonstrate that orderly radiation of pain to the back and downward does not have to be present and that every regional symptom and sign does not have to be in order as the dissection proceeds throughout the aorta. The "violent ache" in the right cheek that spread to the entire anterior part of the chest may warn us that the aneurysm dissected upward — perhaps even to the internal carotid artery to produce the pain in the cheek.

DR. HELEN S. PITTMAN: The patient thought she had a toothache.

DR. PALMER: I am not yet through tracing and explaining these symptoms and signs. The periumbilical pain encourages my belief that I am working on the right answer.

Five hours after the onset of pain, the heart was noted to be quiet, which makes me wonder if the dissection extended backward to involve the coronary arteries. In that event it could have produced infarction or, what I am considering particularly, a rupture into the pericardium. It is too bad that the heart border did not extend well out because then, with a large, quiet heart in the presence of a low blood pressure I should be confident that there was fluid, presumably blood, in the pericardium. We usually assume that the blood pressure remains elevated with dissecting aneurysm. Rupture of an aneurysm may be sudden with the release of blood all at once, or it may result in gradual filling of a rigid, comparatively small space such as the pericardium that, by tamponade, produces shock. This patient's hypotension may have resulted from downward dissection, with rupture and bleeding

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into the pericardium, to compression of coronary arteries or to dissection along the coronary arteries. When the patient entered the hospital she had no signs of congestive heart failure unless the neck veins are considered evidence therefor. How large do neck veins have to be, and do they have to pulsate to denote congestive heart failure? That, I think, is a matter of judgment. If the patient was lying flat in bed when the neck veins were noted to be distended but not pulsating, that was evidence that there was no increased pulmonic pressure. The patient was in actual shock. The nausea and vomiting, I assume, were related to the shock and possibly to the severe pain or to both. It has been my experience that early in shock patients are agitated and awake and have a rapid pulse and rapid, shallow respirations. If the pulse and respirations of the patient under discussion were really normal as stated, I wonder whether she had a lesion in the brain as well as coronary thrombosis or a dissecting aneurysm of the aorta.

Dr. Pittman: When I saw the patient before she entered the hospital, she was agitated, excited and overactive. I could feel no peripheral pulses and could barely make out that her heart was beating. The blood pressure was 70 systolic.

Dr. Palmer: Her pulse was so fast that even Dr. Pittman could not count it!

On the basis of the history and the physical examination I think there are two diagnoses to be considered. The less likely is coronary thrombosis; the more likely is dissecting aneurysm of the aorta, possibly with dissection upward through the great vessels and finally with rupture into the pericardium.

I should like to ask the radiologist two questions: How often can you positively exclude dissecting aneurysm from the x-ray picture, and how often have you made a proved diagnosis of dissecting aneurysm of the aorta? I see a flattish look at the knob of the aorta on the film, and that interests me.

Dr. Stanley M. Wyman: I shall describe the films first and then answer your questions. The heart is greatly enlarged, chiefly in the region of the left ventricle (Fig. 1). The aorta is tortuous in the thoracic portion; its upper margin on the left is "flattish," and its outline is not as sharply defined as usual. Its outline below the heart is clear cut. There may be some pulmonary congestion and there is some scarring in the lung.

Dr. Palmer: Is there any evidence of frank heart failure?

Dr. Wyman: No. There is no fluid in the chest either.

Can we exclude dissecting aneurysm? Certainly not; in fact we should consider it in this case. How often have we made a positive diagnosis of dissecting aneurysm and had it proved? That diagnosis is not commonly suggested. We have made it correctly most often when we have seen angulation with a flattening of the aorta, particularly when it has been in the ascending portion of the aorta. The flattening noted in this case makes us think of dissecting aneurysm, but not as seriously as if it had been in the ascending portion.

Dr. Palmer: Let us continue with the laboratory findings. The +++ test for albumin and the oliguria may be explained by shock. The hemoglobin of 14 gm. per 100 cc. does not rule out bleeding from a ruptured aneurysm because in the early stage before much bleeding has occurred, the hemoglobin may be normal. The normal electrocardiogram is not unusual with dissecting aneurysm.

A white-cell count of 23,800, with 47 per cent neutrophils, 38 per cent monocytes, 6 per cent atypical lymphocytes and 9 per cent lymphocytes, makes me wonder how old a woman must be to be too old for infectious mononucleosis. I have never heard of it in a patient of this age, but I suppose it can happen. Such patients can die suddenly with a ruptured spleen, but I do not for a minute really believe this patient had infectious mononucleosis. She had been unusually fatigued for ten days. Unexpectedly and probably incidental to her fatal illness were found an enlarged liver and spleen, which with the elevated white-cell count and high percentage of monocytes introduce another diagnosis. Lymph-node enlargement was not observed. Last night I looked up the list of conditions in which monocytosis may be present; they are protozoal infections, subacute bacterial endocarditis and the odd infections like brucellosis and tuberculosis. She may have had tuberculosis that suddenly disseminated, but that would not explain the sudden onset of pain and the sudden death although we have all seen older persons with chronic quiescent tuberculosis for years who suddenly have had a dissemination of the process. Such patients may have a rapid septic illness but not a thirty-two-hour episode with sudden pain and shock such as this. I do not believe the patient under discussion had any of these conditions.

The real questions are, How many monocytes are necessary to establish a diagnosis of monocytic leukemia, and, if the patient did have monocytic leukemia did it have any relation to the disease that caused her death? Dr. Pittman, is it not usually difficult for you or Dr. Jacobson or anyone to be certain of the diagnosis of monocytic leukemia?

Dr. Pittman: It was not a bit difficult for Dr. Jacobson in this case.

Dr. Palmer: I had thought that the more one knew about blood cells, the harder it was to decide how far down the stem each cell belonged. In general, to make a diagnosis of monocytic leukemia, I would fancy at least 50 per cent monocytes. Yet Dr. Pittman and Dr. Jacobson were certain of the diagnosis with only 38 per cent.

DR. BENJAMIN CASTLEMAN: Another smear showed a higher percentage of monocytes and was reported as being an unequivocal demonstration of monocytic leukemia.

DR. PALMER: Then was this disease incidental, or did it contribute to the patient's death? Leukemia can infiltrate almost anywhere. In the spleen and elsewhere it infiltrates the perivascular spaces. Perhaps it was infiltrating throughout the mediastinum and had involved the aorta and the great vessels; then it may remotely have contributed to the dissecting aneurysm.

Before I conclude, I should like to ask what kind of stimulant the patient was given when she was admitted. I hope it was not epinephrine. Perhaps it was Neosynephrine.

DR. CASTLEMAN: Neosynephrine.

DR. PALMER: That, I think was a proper stimulant to use. I wonder why digitalis was given. I should not expect it to have been effective. It was probably a conscience dose.

My diagnoses are dissecting aneurysm with dissection upward, perhaps far enough to cause cerebral circulatory insufficiency, and downward perhaps to involve the coronary arteries and compress them; old coronary thrombosis; and monocytic leukemia.

CLINICAL DIAGNOSES

Pulmonary embolus.
?Myocardial infarct.
Monocytic leukemia.

DR. ROBERT S. PALMER'S DIAGNOSES

Dissecting aneurysm of aorta.
Coronary-artery disease, old, with thrombosis.
Monocytic leukemia.

ANATOMICAL DIAGNOSES

Ruptured dissecting aneurysm of aorta into pericardium.
Monocytic leukemia.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: We have recently sent a questionnaire to some of the medical students throughout the country who read the Case Records; in one of the comments a student asked, "Why do you have so many dissecting aneurysms? Are they that common?" The answer is yes, and this case is another example of one.

We found the pericardial cavity filled with about 400 cc. of blood, forming a tamponade. The intimal tear was in the ascending aorta about 4 or 5 cm. above the aortic valve. The dissection extended as far as the origin of the innominate artery but no farther so that there could not have been any occlusion of the carotid arteries. It also surrounded the mouths of the coronary vessels but did not dissect into them. Although we could not find the adventitial tear that produced the hemopericardium it was probably at the level of the intimal tear. We thought that there had probably been a slow ooze and finally a rapid hemorrhage. The blood had extended into the mediastinum, surrounding the pulmonary artery and extended—one might call it a dissection—along the adventitia of the pulmonary arteries into the lung. That is not an infrequent finding with ruptured aortic aneurysm. It is amazing how fast that must have occurred because it probably occurred just before death; within a matter of minutes the adventitial dissection went all the way into the lungs. There was no myocardial infarction as the result of the narrowing of the coronary mouths and very little arteriosclerosis in the coronary arteries. The heart was enlarged, weighing 450 gm., so that hypertension may have developed after the examination eight years before admission.

The bone marrow showed monocytic leukemia, which, as Dr. Palmer suggested, was an incidental finding. We saw no leukemic infiltration around the aorta. The liver was enlarged, with extensive foci of necrosis, but there, also, we could not find any leukemic cells. We do not know what the cause of the necrosis was.

The spleen was enormous, weighing 1000 gm., and contained many areas of necrosis and probably leukemic cells although there was so much necrosis that we could not be sure.

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ANTIBIOTICS, STAPHYLOCOCCAL ENTERITIS AND PSEUDOMEMBRANOUS ENTEROCOLITIS

EVER since the broad-spectrum antibiotics gained wide acceptance, there has been much concern about the gastrointestinal complications that accompany their administration. Although nausea, vomiting, frequent or bulky stools and diarrhea have been accepted as unavoidable and annoying, and have sometimes made it necessary to discontinue treatment, they have not been considered serious. Recently, however, some of the diarrheas have proved to be unusually severe, intractable and accompanied by shock and dehydration; they have also been contributing factors, if not the actual cause, in some deaths. The staphylococcus has been implicated in some of these cases; in others the antibiotics have been regarded as responsible for the symptoms and the pathological finding of pseudomembranous enterocolitis.

In 1939 Penner and Bernheim[1] reported 40 autopsied cases of acute ulcerative or diphtheritic colitis from Mount Sinai Hospital in New York City. The lesions were found after abdominal operations, mastectomy and lobectomy and in unoperated patients with burns or gastrointestinal hemorrhages. A common denominator in these cases was shock, and the lesions were reproduced in animals in which shock had been induced by various means. Pulmonary edema was also present in the human patients and in the animals; however, intubation was not a predisposing factor except when carried out in patients with shock.[2] The value of prevention by early and intensive treatment of the shock and diarrhea was stressed.

In 1948 Dixon and Weismann[3] presented 23 cases of acute pseudomembranous enteritis or enterocolitis complicating intestinal surgery observed during a seven-and-one-half-year period beginning in 1940. No significant pathogens were found, but in 10 of 20 cases autopsy showed frank peritonitis, either generalized or local. The clinical picture was that of progressive circulatory collapse merging with irreversible shock, followed by death within a few hours. Other symptoms, each noted in 9 to 13 patients, were abdominal pain, vomiting, fever, abdominal distention and diarrhea. The condition often resembled Asiatic cholera and was thought to have a similar basis. The diagnosis was made during life in 4 patients; it was verified at autopsy in 2, and in the survivors typical membranous casts were later observed in the feces. Most of the patients in this series had received sulfonamides (presumably, sulfaguanidine or succinylsulfathiazole) in preparation for bowel surgery.

Hilsabeck and Dixon[4] recently reported a case in which the condition was suspected and the patient apparently responded to prompt and intensive antishock therapy and control of electrolyte balance. The patient later died of a pulmonary embolus, and the characteristic lesions in the process of healing were demonstrated at autopsy.

Kleckner, Bargen and Bagenstoss[5] reviewed the records of the Mayo Clinic for the years 1940–50 and found 14 cases of pseudomembranous enterocolitis not preceded by an operation. These lesions were considered to be the immediate cause of death in 7 cases. Neoplasms of the bowel with obstruction were present in 5, cardiac lesions in 5 others and severe infections (pneumonia, peritonitis, meningitis and streptococcal septicemia) in the remaining 4. No increase in the incidence of fatal acute postoperative pseudomembranous enterocolitis was observed since the intestinal lesions had been treated with chemotherapeutic or antibiotic agents, which were therefore not believed to be implicated in the pathogenesis of the lesion.

In contrast, Reiner, Schlesinger and Miller[6] described 7 cases of pseudomembranous enterocolitis in which aureomycin and chloramphenicol were emphatically declared to be the cause of the lesions, which had followed the use of these antibiotics. They found no other significant etiologic agent in these cases.

The relation of the staphylococcus to severe intestinal reactions has also been emphasized recently. Jackson et al.[7] reported that 37 of 91 patients treated with terramycin for pneumonia had diarrhea with or without vomiting; cultures of the stools were made in 18 of these patients and in 12, *Staphylococcus aureus* resistant to penicillin, terramycin and aureomycin was found as the only or the predominant organism in the watery feces. Staphylococcal diarrhea may have been an important contributing factor in the fatal outcome of at least 3 of these patients. Similar cases of staphylococcal enteritis had been reported by the same authors in patients treated with this and other antibiotics for other infections [8, 9] and in some patients who had not received antibiotics.[8]

In a study on the antibiotic resistance of pathogenic staphylococci at the Boston City Hospital, Finland and Haight[10] included 33 strains that were obtained as the sole or predominant organism in the feces of patients with severe diarrhea, most of them complicating terramycin therapy. All the strains were highly sensitive to erythromycin, but 91 per cent were highly resistant to penicillin, 64 per cent to aureomycin and 79 per cent to terramycin. In 1 patient administration of erythromycin and discontinuance of terramycin resulted in prompt clinical improvement, with elimination of the staphylococci from the stools.[11] However, similar favorable results had been obtained by Jackson et al.[7] in some cases when terramycin was discontinued promptly after recognition of the severe diarrhea and either supportive therapy alone instituted or aureomycin intravenously or penicillin intramuscularly given in addition.

In Montpellier, France, Janbon and his associates[12] observed 9 patients who manifested a choleriform reaction associated with staphylococci during terramycin treatment for various infections. Most of these patients recovered promptly when the drug was stopped and symptomatic treatment was instituted. Similar cases, some of them fatal, have been ascribed by various observers to staphylococcal infections complicating therapy with terramycin and other antibiotics.

Recently, in a report that received considerable newspaper and radio publicity, Dr. P. T. Sloss, of the Mayo Clinic, called attention to the problem raised by the staphylococcal diarrheas observed in patients receiving antibiotics. The choleriform syndrome was ascribed to an "enterotoxemia" produced by the overgrowth of resistant staphylococci after suppression of normal bowel flora by the potent antibiotics.[13] Some of the data upon which this report was presumably based have now been discussed by Dearing and Heilman,[14] who presented 44 patients, in 43 of whom staphylococci were found in fecal cultures; 39 of these patients had received terramycin; succinylsulfathiazole, penicillin in addition to dihydrostreptomycin, and aureomycin had each been used in 1 patient, and 2 had had no antibacterial therapy. The susceptibility of the strains to antibiotics was similar to that reported by Finland and Haight.[10] Some of the patients had only a few micrococci and predominantly normal intestinal flora at the time of operation, but most of them had staphylococci in large numbers — some in pure cultures in the intestinal content. Some of those with a small number of staphylococci and

a few in whom those organisms were predominant had no symptoms and required no treatment except discontinuance of the terramycin; in others, however, diarrhea and other severe symptoms developed during this therapy or after the antibiotic had been discontinued, and in such cases the diarrhea and symptoms cleared and the staphylococci disappeared from the feces only after erythromycin had been given.

There were also 6 fatal cases of pseudomembranous enterocolitis, 5 of them proved at autopsy; staphylococci were found in the feces either at operation or at post-mortem examination in 5. Terramycin had been used in 5 cases (intravenously alone in 2), and aureomycin in 1. A seventh patient, who had received terramycin intravenously before operation, had staphylococcal peritonitis. In none of these fatal cases had erythromycin been used. Because of the absence of staphylococci in 1 case and because a review of the autopsy records at the Clinic revealed that between 1927 and 1936, inclusive, when no antibiotic agents were available, 42 patients had died of pseudomembranous enterocolitis, whereas from 1943 to 1952, inclusive, during the antibiotic era, only 37 patients had died of a similar lesion, it was concluded that neither the staphylococcus nor the antibiotics were necessarily related to the pseudomembranous enterocolitis.

From all these observations it seems reasonable to conclude that there are two important and distinct entities. One is the pseudomembranous enteritis or enterocolitis that chiefly follows operations on the bowel but may occur in patients with lesions of the bowel without such operations and occasionally in other types of cases. Since such patients are frequently given chemotherapy or antibiotics at about the time when this syndrome may occur, it has quite naturally been ascribed to this therapy; however, the syndrome certainly occurs independently of such therapy. The possibility that antibiotics either condition its occurrence or aggravate the symptoms has not been proved, but if the broad-spectrum antibiotics are considered to be contributing factors in the occurrence of pseudomembranous enterocolitis, other antimicrobial agents, including streptomycin and the poorly absorbed sulfonamide drugs, must also be implicated. The failure to correlate this lesion with antibiotic therapy has recently been re-emphasized by workers at the Mayo Clinic.[16]

Staphylococcal enteritis appears to be a separate and distinct entity with some manifestations similar to those of pseudomembranous enterocolitis; the finding of staphylococci in large numbers or in pure culture in the watery feces is the crucial feature. Both conditions may be described clinically as "enterotoxemias," but no true enterotoxin has yet been demonstrated either in the fecal content or in the staphylococcal cultures. The findings in the staphylococcal cases resemble those of certain severe acute salmonella infections and those of cholera, and the pathology may be quite similar. The great majority of the recently reported cases of staphylococcal enteritis had been treated with terramycin, but some were treated with aureomycin or other antibacterial agents and others had received no antibiotics. An example of such a case following terramycin administration is presented elsewhere in this issue as Case 39271 of the Case Records of the Massachusetts General Hospital.

Therapy of the staphylococcal diarrheas includes prompt discontinuance of the offending antibiotic as soon as the condition has been recognized, and institution of intensive symptomatic therapy is often sufficient to relieve the condition; erythromycin administration has also caused prompt disappearance of symptoms and elimination of the staphylococci from the stools. Other nonabsorbed or poorly absorbed antibiotics to which the staphylococci are susceptible (for example, bacitracin and neomycin) may be effective. It is not clear, however, whether pseudomembranous enterocolitis can be either prevented or cured by any means other than intensive symptomatic treatment instituted at the earliest possible moment; if antibiotics, which may themselves produce or aggravate an existing diarrhea, are being given by mouth when the condition is recognized, they should, of course, be discontinued. Early recognition and prompt action is essential if fatal cases are to be avoided.

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MAINE MEDICAL ASSOCIATION 1853–

HAVING recently congratulated the Texas Medical Association on attaining its hundredth birthday, the *Journal* now grasps the opportunity of extending similar felicitations to an almost next door neighbor. But the youngest state in New England is something more than a neighbor to Massachusetts, besides being practically antipodal to Texas. In 1820, being then a living, pulsing part of the Bay State it separated from the other section of its substance like the splitting of a personality or a cell undergoing mitosis, leaving the lesser half behind.

When Maine thus separated from Massachusetts, only sixteen years before Texas effected her somewhat ruder separation from Mexico, its physicians who had been fellows of the Massachusetts Medical Society continued their fellowship as a Maine Medical Society. Trouble seemed to dog the footsteps of this organization, however. There was dissension among the officers, bad traveling conditions prevented regular attendance and Dr. James A. Spalding, who some years ago memorialized in a small volume the Maine physicians of 1820, even hinted at an excess of conviviality that might have interfered with the more serious aspects of the society's gatherings.

Whatever the reason, the Maine Medical Society dissolved about 1845, leaving the way clear for the founding of the current Maine Medical Association in 1853, the celebration of its centennial in June, 1953, and the congratulations to the Maine Association of the *New England Journal of Medicine*, which are hereby tendered.

By a slight change of voice and time the cry "Remember the Alamo" becomes consonant with the later battle slogan, "Remember the Maine."

CHEMOPROPHYLAXIS AGAINST INFECTIONS WITH THE HEMOLYTIC STREPTOCOCCUS

PERHAPS the most successful demonstration of the efficacy of mass chemoprophylaxis was the virtual elimination of meningococcal meningitis and meningococcal carriers from certain military installations in the United States during World War II; this was accomplished simply by the simultaneous administration of as little as 1 or 2 gm. of sulfadiazine daily for only one or two days to the entire personnel of the stations concerned. Such a result was possible chiefly because of the marked sensitivity of the meningococcus to sulfadiazine, although other factors, less well understood, may have been involved. Similar attempts to influence the prevalence of infections due to the hemolytic streptococcus with sulfadiazine indicated that continuous administration of the drug for longer periods was needed and even then they were much less successful. Moreover, the efficacy of this type of prophylaxis was practically nullified in several military installations when virulent hemolytic streptococci that were quite resistant to sulfadiazine appeared and spread in epidemic proportions during this program of prophylaxis. The poorer result of sulfonamide prophylaxis against the infections could be ascribed, in part, to the fact that even susceptible streptococci are, in general, much less sensitive to sulfadiazine than meningococci are; it is also consistent with many indications that even when full therapeutic doses of sulfadiazine are used, susceptible strains of hemolytic streptococci are difficult to eradicate, both from patients and from carriers.

Penicillin, however, is highly effective against virulent Group A streptococci; indeed, among the common human pathogenic bacteria, only the gonococcus is more susceptible to that antibiotic.

In addition, it has been possible to eradicate hemolytic streptococci from patients and carriers by treatment with penicillin provided that adequate doses are given and the treatment is continued for seven to ten days. Moreover, strains of Group A hemolytic streptococci of even moderate resistance to penicillin have not been encountered in active human infections. It therefore seems reasonable to expect that penicillin may prove more effective than sulfonamides in critical situations when it is urgently desired to prevent or terminate epidemics of such infections.

Two reports of studies on the effectiveness and feasibility of penicillin prophylaxis are now available, one from the United States Naval Training Center in Bainbridge, Maryland,* and the other, presented elsewhere in this issue of the *Journal*, from the Francis E. Warren Air Force Base in Wyoming. The Bainbridge project was undertaken in February, 1952, at, or just after, the peak of an epidemic of acute respiratory diseases. Although part of the study included parallel observations in controls chosen at random (some receiving sulfadiazine and others aspirin) its value was considerably reduced by certain features. During the prophylactic program there was a sharp decline in the incidence of respiratory disease even in the control groups; this decline coincided with the beginning of the prophylactic program and may have been attributable, in part, to it. In addition, throat washings and throat cultures made on a representative sampling of acutely ill patients just before the program was instituted revealed that approximately 30 per cent of the throat cultures were positive for beta-hemolytic streptococci, and over a third of the throat washings were subsequently found positive for strains of influenza virus. Also, when the prophylactic study was in progress all patients with acute respiratory disease were hospitalized, whereas previously only those who were severely ill had been hospitalized; this, too, may have influenced the incidence of streptococcal infections among the study groups. The report from Wyoming deals with a large-scale study done in the spring of 1951 and with small "pilot" studies done during the preceding and following winters.

In the Navy's study the placebo of aspirin was given in a dose of 0.3 gm. daily for two weeks and the sulfadiazine in doses of 1 gm. daily, also for 2 weeks, whereas the buffered penicillin was given orally in doses of 125,000 units daily for four weeks. All doses were given in midmorning for the first four days, but subsequently they were given at reveille. An analysis of the Bainbridge experiences was interpreted as warranting the following conclusions: sulfadiazine was more effective than penicillin against nonstreptococcal respiratory diseases; penicillin and sulfadiazine were equally effective against streptococcal respiratory disease; and penicillin was more effective than sulfadiazine in decreasing the prevalence of streptococci in the general population. In that study there was no evidence of the development of strains of streptococci resistant to either penicillin or sulfadiazine. No serious reactions to any of the drugs were encountered; the incidence of dermal reactions to penicillin was 1:300, to sulfadiazine 1:450 and to aspirin 1:2000. Although during the course of this epidemic 27 cases of acute glomerulonephritis were diagnosed clinically and perhaps a few additional ones were not recognized, the effect of the prophylaxis on the occurrence of this complication could not be evaluated.

In the study from the Warren Air Force Base much larger doses of penicillin were given, and the intramuscular route was used in some of the pilot studies. In this study oral doses of 250,000 units of buffered crystalline penicillin daily for ten days did not suppress or eradicate the carrier state in many men harboring Group A hemolytic streptococci. Likewise, a single intramuscular injection of a depot type of penicillin (600,000 units of procaine penicillin in oil and aluminum monostearate) failed to eradicate Group A streptococci. A similar amount of benzethacil, another depot form of penicillin, though apparently more successful than the procaine penicillin, failed to eliminate streptococci from some nasal carriers and to prevent the acquisition of new types in occasional persons. On

*Gezon, H. M., Cook, J. S., Magoffin, R. L., and Miller, C. H. Use of penicillin and sulfadiazine as prophylactic agents against streptococcal and non-specific respiratory infections among recruits at Naval training center. *Am. J. Hyg.* 57:71-100, 1953.

the other hand, four doses of 600,000 units each of procaine penicillin given every other day or 1,800,000 units of the benzethacil given as two simultaneous injections was more effective in maintaining a carrier-free state. To achieve similar results with the oral route, it was necessary to give penicillin in doses of 1,000,000 units twice daily for ten days, although perhaps half that amount was also effective.

The workers at the Warren Air Force Base succeeded in reducing the rates of streptococcal disease and of carriers for periods of two or three weeks in large groups of men who received 1,000,000 units of penicillin orally twice daily for five or ten days; the longer treatment period had a somewhat more sustained effect. These larger doses of penicillin produced diarrhea quite frequently — probably as frequently as is usually reported from the use of the broad-spectrum antibiotics. In about 1 per cent of the men receiving penicillin for ten days definite skin reactions were observed, and a few others had questionable skin reactions; reactions were less frequent in the men who received the drug for only five days.

Although it is encouraging to know that the incidence of streptococcal infection and perhaps the severity of epidemics of streptococcal disease can to some extent be reduced, the results of these studies may be considered disappointing in certain respects. Large-scale uses of parenteral injections for prophylaxis would certainly not be desirable even if they were feasible. From the Warren Air Base study it seems that large doses, given for about ten days, would be necessary if the oral route was used. Such large doses are not innocuous, and their sensitizing effect may not be fully appreciated until the recipients require penicillin at some later time; their use may also be conducive to the establishment and spread of penicillin-resistant organisms. Moreover, although penicillin in both studies proved more effective than sulfadiazine in suppressing or eliminating streptococcal carriers, it cannot yet be stated unequivocally that penicillin is always a better prophylactic agent than sulfadiazine against streptococcal infections. Indeed, there is some suggestion from the Bainbridge studies that sulfadiazine may be preferable for short periods of chemoprophylaxis from the point of view of activity, toxicity and economy, in epidemics of acute respiratory infections when only sulfonamide-sensitive strains of hemolytic streptococci are prevalent.

A Cincinnati druggist recently, while asleep, swallowed a gold plate, upon which false teeth had been inserted. The plate lodged a short distance below his palate, and will neither go up or down. It causes him great pain, and it is feared that lockjaw will ensue.

Boston M. & S. J., *June 29, 1853*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

SMITH-PETERSEN — Marius N. Smith-Petersen, M.D., of Boston, died on June 16. He was in his sixty-eighth year.

Dr. Smith-Petersen received his degree from Harvard Medical School in 1914. He was chief of orthopedic surgery at the Massachusetts General Hospital from 1935 to 1946. He was a member of the American Orthopaedic Association, the American Academy of Orthopaedic Surgeons and the New England Surgical Society, and a fellow of the American College of Surgeons and the American Medical Association.

He is survived by his widow, two sons, a daughter and seven grandchildren.

BOOK REVIEWS

New Outlook on Mental Diseases. By F. A. Pickworth, M.B., B.Sc. 4°, cloth, 296 pp., with 41 illustrations. Baltimore: Williams and Wilkins Company, 1952. $12.00.

This book contains the latest information from the battleground where that great struggle concerning the body versus the mind is going on. It is a communiqué reporting the newest facts about the body systems, much of it up to the minute. It is very well organized and has an excellent spacious format and illustrations. Although this book would be most valuable to physicians, the vast number of important data concerning the various parts of the body that it contains classify it as a volume useful for reference and research workers. The color prints are excellent.

Of particular interest are two chapters — one on the theory of treatment and one on the nature of the mind.

MERRILL MOORE, M.D.

This is Your World: A book for the orientation of professional workers to the emotional problems of the chronically ill patients: Tuberculosis and the individual. Written and illustrated by Harry A. Wilmer, M.D., Ph.D. With a foreword by Adelaide McF. Johnson, M.D., Ph.D. 8°, cloth, 165 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1952. $5.50. (Publication No. 140, *American Lecture Series.*)

This is a new kind of book that will prove to be of special interest for all professional workers concerned with the emotional problems of the chronically ill, particularly of patients with tuberculosis. It is a human book, full of facts (some quite original) and interesting diagrams that are graphic and revealing. It is also a thought-provoking book not for physicians alone but for all who come in contact with chronic invalids.

MERRILL MOORE, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Josiah Macy, Jr., Foundation publishes a number of series of conferences on medical subjects. The following are the latest issues. Complete sets of these valuable reference sources should be in all medical libraries, and the individual volumes are of value to specialists in the various subjects.

Adrenal Cortex: Transactions of the Third Conference, November 15-16, 1951, New York, New York. Edited by Elaine P. Ralli, M.D., Department of Medicine, New York University College of Medicine. 8°, cloth, 204 pp., with 58 illustrations. New York: Josiah Macy, Jr., Foundation, 1952. $3.25.

Connective Tissues: Transactions of the Third Conference, February 14-15, 1952, New York, New York. Edited by Charles Ragan, M.D., Department of Medicine, Columbia University College of Physicians and Surgeons. 8°, cloth, 166 pp., with 50 illustrations. New York: Josiah Macy, Jr., Foundation, 1952. $3.50.

Liver Injury: Transactions of the Eleventh Conference, April 30 and May 1, 1952, New York, New York. Edited by F. W. Hoffbauer, M.D., associate professor of medicine, University of Minnesota Medical School and Minnesota Hospitals, Minneapolis. 8°, cloth, 265 pp., with 96 illustrations. New York: Josiah Macy, Jr., Foundation, 1953. $4.00.

Nerve Impulse: Transactions of the Third Conference, March 3 and 4, 1952, New York, New York. Edited by H. Houston Merritt, M.D., professor of neurology, Columbia University College of Physicians and Surgeons. 8°, cloth, 176 pp., with 16 illustrations. New York: Josiah Macy, Jr., Foundation, 1952. $3.50.

Problems of Aging: Transactions of the Fourteenth Conference, September 7-8, 1951, St. Louis, Missouri. Edited by Nathan W. Shock, M.D., chief, Section on Gerontology, National Heart Institute, National Institutes of Health, and Baltimore City Hospitals. 8°, cloth, 138 pp., with 7 tables. New York: Josiah Macy, Jr., Foundation, 1952. $3.00.

Renal Function: Transactions of the Third Conference, October 18-19, 1951, New York, New York. Edited by Stanley E. Bradley, M.D., Department of Medicine, Columbia University College of Physicians and Surgeons. 8°, cloth, 210 pp., with 80 illustrations and 11 tables. New York: Josiah Macy, Jr., Foundation, 1952. $3.50.

Shock and Circulatory Homeostasis: Transactions of the First Conference, October 22-23, 1951, New York, New York. Edited by Harold D. Green, M.D., professor of physiology and pharmacology, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, North Carolina. 8°, cloth, 245 pp., with 24 illustrations and 8 tables. New York: Josiah Macy, Jr., Foundation, 1952. $3.50.

Advances in Internal Medicine. Vol. 5. Edited by William Dock, M.D., Long Island College of Medicine, Brooklyn; and I. Snapper, M.D., Mount Sinai Hospital, New York City. 8°, cloth, 464 pp., with illustrations. Chicago: Year Book Publishers, Incorporated, 1952. $10.50.

This new volume of a standard reference series discusses the subjects of diseases of the pregnant woman affecting the offspring, catheterization of the heart, portal hypertension and its treatment, the anemia of infections, gout, a derangement of purine metabolism, clinical aspects of ganglionic and adrenergic blocking agents, aspects of the influenza problem, experiences with ACTH and cortisone, and abnormal proteins in myeloma. The various articles provide surveys of the current knowledge of the subjects discussed. Extensive bibliographies are appended to the articles; there are indexes of authors and subjects, and the publishing is good. This type of reference work should be in all medical libraries.

The Haunted Pound and Other Poems. By John Franklin Holmes, M.D. 12°, cloth, 64 pp. New York, New York: Exposition Press, 1952. $2.00.

Dr. Holmes, a poet-physician of Massachusetts, has brought together a selection of his short poems under the headings of: "At Peace with the Toilers," "Consider the Day," "The Road over Which We Have Journeyed," "When Father Takes His Bath" and "In Our Day." The small book should be in all collections of poetry by physicians.

Die körperlichen Bedandlungsverfahren in der Psychiatrie: ein Lehr-und Handbuch. Band I: Die Insulinbehandlung. By Dr. Max Müller, professor of psychiatry, Universität Bern. 8°, cloth, 295 pp., with 4 illustrations and 20 tables. Stuttgart: Georg Thieme, 1952. DM 36.–. (Distributed by Grune and Stratton, New York.)

In this first volume of a treatise on the physical treatment of mental disorders Dr. Müller discusses the use of insulin. The text is divided into three parts: technic of treatment; pathophysiology and psychopathology; on prognosis, special indications and the theory of treatment. The literature has been reviewed, and the coverage is extensive in scope. There is a bibliography of 31 pages and extensive indexes of authors and subjects. The publishing is excellent; the book should be in all collections on psychiatry and insulin.

Acute Peripheral Arterial Occlusion. By William D. Holden, M.D., Oliver H. Payne Professor of Surgery, Western Reserve University School of Medicine, and director of surgery, University Hospitals of Cleveland. 8°, cloth, 66 pp., with 2 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $2.35. (Publication No. 141, *American Lecture Series.*)

This concise monograph discusses the etiology, hemodynamic changes, clinical manifestations and management of acute arterial occlusion.

The Old Egyptian Medical Papyri. By Chauncey D. Leake, vice-president, University of Texas — Medical Branch, Galveston. 8°, cloth, 108 pp., with 15 tables. Lawrence, Kansas: University of Kansas Press, 1952. $1.00. (Logan Clendening Lectures on the History and Philosophy of Medicine, Second Series.)

Dr. Leake in this series of lectures discusses the known medical papyri in general and the Hearst Medical Papyrus in particular. The various papyri are listed, and there is a bibliography and an index. The publishing is excellent. The small volume should be in all history collections, medical and general.

Refresher Course for General Practitioner: Specially commissioned articles from the British Medical Journal. First collection, October 1949 to December, 1950. 8°, cloth, 502 pp., with illustrations. London: British Medical Association, 1952. 25 shillings.

The articles comprising this series, covering many fields of medicine, have been written by acknowledged experts and have been revised and brought up to date. They have been republished in a volume to meet the desire expressed by a number of physicians. An index has been provided, and the publishing is excellent. The book should prove interesting to the practicing physician.

Besinnung und Bewusstsein: Persönlichkeitsaufbau und Persönlichkeitszerfall aus psychologischpädagogischer, soziologischer und psychiatriascher Sicht. By G. E. Störring, Dusseldorf. 8°, paper, 134 pp. Stuttgart: Georg Thieme, 1953. DM 11. (Distributed by Grune and Stratton, New York.)

This small monograph on consciousness is divided into normal psychology and psychopathology. The last part contains a number of case histories and a special chapter on schizophrenia. The literature is noted, and there is a bibliography of five pages.

The Obstetrical and Gynaecological Literature: Published in Finland from 1901 to 1950. By Olavi Kinnunen and Kalevi Niemineva. 8°, paper, 118 pp. Helsinki, 1951. Mk 600:–(*Medicina Fennica,* Supplement No. 1, 1951.)

This supplement to a well known Finnish medical journal is interesting because of its tabulation of the articles on obstetrics and gynecology, written in Finland during the ten years before 1951. They total 2314 items. There is a supplement listing the writings of obstetricians and gynecologists in other fields of medicine.

Analgesia and Anesthesia in Obstetrics. By J. P. Greenhill, M.D., professor of gynecology, Cook County Graduate School of Medicine, attending gynecologist, Cook County Hospital, attending obstetrician and gynecologist, Michael Reese Hospital, and member, associate staff, Chicago Lying-in Hospital, Chicago. 8°, cloth, 85 pp., with 16 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $2.75. (Publication No. 159, *American Lecture Series.*)

In this small monograph the author discusses the various modes of anesthesia and inhalation agents used in obstetrics. There is a short bibliography and a good index.

Poliomyelitis: Papers and discussion presented at the Second International Poliomyelitis Conference. Compiled and edited for the International Poliomyelitis Congress. 4°, cloth, 555 pp., with illustrations. Philadelphia: J. B. Lippincott Company, 1952. $7.50.

This volume presents the various papers read at the Second International Poliomyelitis Conference, held at the University of Copenhagen in 1948. The material is divided into different symposiums and reviews: the virus and its interaction with the host cell, pathology and pathophysiology of poliomyelitis, the Coxsackie group of viruses, differential diagnosis in acute poliomyelitis and treatment, immunity and ecology of poliomyelitis. A large number of scientific exhibits are listed and described. There is a good index, and the volume is well published. It should be in all medical libraries and in all collections on the subject.

Office Management of Ocular Diseases. By William F. Hughes, Jr., M.D., professor of ophthalmology and head, Department of Ophthalmology, University of Illinois College of Medicine, ophthalmologist in chief, Illinois Eye and Ear Infirmary, and attending ophthalmologist, Presbyterian Hospital, Chicago. 8°, cloth, 452 pp., with 120 illustrations and 52 tables. Chicago: Year Book Publishers, Incorporated, 1953. $9.00.

This book discusses the various disorders of the eyes that may be treated in the office. Beginning with vision and refraction, the author considers the whole field of ophthalmology, including injuries, with special chapters on radiation treatment and with the ophthalmic formulary. Selected lists of references are appended to the chapters. There is a good index, and the book is well published.

Alcoholism, 1941-1951: *A survey of activities in research, education and therapy.* By the staff of The Yale Center of Alcohol Studies. 4°, paper, 90 pp. New Haven: *Quarterly Journal of Studies on Alcohol,* 1952.

This pamphlet, which is a reprint from the *Quarterly Journal of Studies on Alcohol,* presents in separate form seven papers dealing with various aspects of alcoholism.

Down the Ridge. By W. L. White. 8°, cloth, 180 pp. New York: Harcourt, Brace and Company, 1953. $3.00.

Mr. White, in this graphic story, tells how the wounded in Korea are transferred to a mobile army surgical hospital and, through various stages, to Tokyo and back to the United States. The book is well published and should find a place in the literature of military medicine.

Living with Diabetes. By Edward Tolstoi, M.D. 8°, cloth, 87 pp. New York: Crown Publishers, Incorporated, 1952. $2.00.

In this small popular book Dr. Tolstoi explains the "normal living" treatment of diabetes that he has used during the past fifteen years.

NOTICES

GRANTS IN CANCER RESEARCH

The American Cancer Society, through the Committee on Growth of the National Research Council, announces that applications for grants-in-aid are now being accepted. Applications for new grants that are received before October 1 will be considered during the winter, and grants that are then recommended will become effective July 1, 1954.

Approximately 250 grants, totalling more than $1,700,000, have been awarded during the past year by the American Cancer Society, on the recommendation of the Committee on Growth.

Application blanks and additional information may be obtained from the Executive Secretary, Committee on Growth, National Research Council, 2101 Constitution Avenue, Washington 25, D. C.

BOSTON CITY HOSPITAL PEDIATRIC GRAND ROUNDS

The Pediatric Grand Rounds held on Tuesdays in the Cheever Amphitheater of the Dowling Building, Boston City Hospital, have been canceled for the summer and will resume on September 1, at 12 noon.

INSTITUTE ON TEACHING AND IMPROVING ESOPHAGEAL SPEECH

An institute on teaching and improving esophageal speech will be held at the Cleveland Hearing and Speech Center, Cleveland, Ohio, August 10 through 16. This institute, the second on voice pathology, is being sponsored by the American Cancer Society, National Cancer Institute of the National Institutes of Health, Office of Vocational Rehabilitation, Cleveland Otolaryngological Society, Cleveland Academy of Medicine and Western Reserve University School of Medicine.

Nationally known surgeons, speech pathologists and lay teachers of esophageal speech will conduct lectures and demonstrations and supervise practice in teaching esophageal speech. Fluoroscopic views will be used to facilitate studies of the physiology of esophageal speech.

Nonspeaking laryngectomized persons are invited to attend the institute without charge. They may be sent by surgeons, cancer societies, societies for crippled persons and rehabilitation services.

Surgeons, speech pathologists and lay persons are invited to attend the sessions. Limited registration is necessary. Application must be made by July 15 to Warren H. Gardner, Ph.D., program chairman, 11206 Euclid Avenue, Cleveland 6, Ohio.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The next scheduled examination (Part 1), written, for all candidates will be held in various cities of the United States and Canada on Friday, February 5, 1954.

All candidates for admission to the examination for certification by the Board are required to submit with their application, a plain typewritten list of all patients admitted to the hospitals where they practice, for the year preceding their application or the year before their request for reopening of their application, with the diagnosis, pathological diagnosis, nature of treatment and end result. Twenty-five case abstracts are due immediately after notification of eligibility and are to be sent by the candidate to the Secretary.

Attention of all candidates is called to a change in date. Application for examination or re-examination, as well as requests for resubmission of case reports, must be made to the Secretary before October 1, 1953.

Requests for application forms for appraisal of incomplete training and for certification, and bulletins should be made to Robert L. Faulkner, M.D., secretary, American Board of Obstetrics and Gynecology, 2105 Adelbert Road, Cleveland 6, Ohio, and should be accompanied by a large self-addressed, stamped envelope.

WEST VIRGINIA STATE MEDICAL ASSOCIATION

The annual meeting of the West Virginia Medical Association will be held at the Greenbrier, White Sulphur Springs, July 23-25.

SECOND INTERNATIONAL CONGRESS OF CARDIOLOGY

The Second International Congress of Cardiology will meet September 12-15, 1954, in Washington, D. C. The annual scientific sessions of the American Heart Association will follow immediately, September 16-18.

The local heart association in the various localities of the United States and Canada have arranged a series of post-congressional visits and conferences to at least twenty of the leading cardiac clinics.

(*Notices concluded on page xi*)

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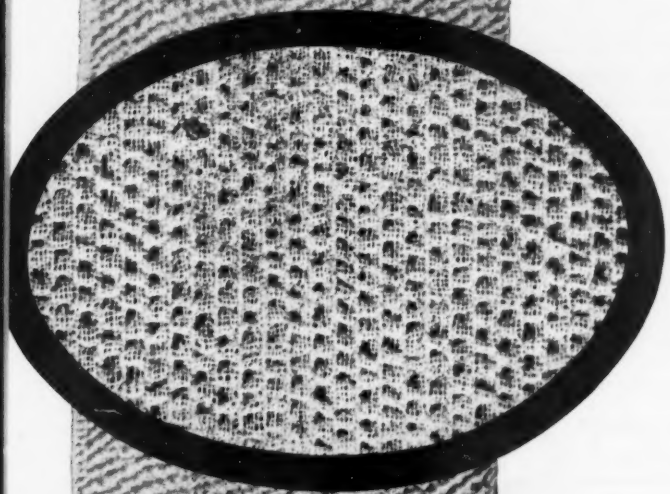

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SOCIETY MEETINGS AND CONFERENCES

JULY 23–25. West Virginia State Medical Association. Page 44.

AUGUST 10–16. Institute on Teaching and Improving Esophageal Speech. Page 44.

AUGUST 18–21. Third International Congress of Electroencephalography and Clinical Neurophysiology. Page 707, issue of April 16.

OCTOBER 4–9. American Academy of Pediatrics. Page 1126, issue of June 25.

OCTOBER 17–20. American Association of Blood Banks. Page 1126, issue of June 25.

OCTOBER 19–30. New York Academy of Medicine. Page xvii, issue of June 11.

OCTOBER 28. New England Obstetrical and Gynecological Society. Page 868, issue of November 27.

SEPTEMBER 12–15, 1954. Second International Congress of Cardiology. Page 44.

SEPTEMBER 16–18, 1954. American Heart Association. Annual Scientific Sessions. Page 44.

DISTRICT MEDICAL SOCIETY

MIDDLESEX EAST

SEPTEMBER 23.

NOVEMBER 18.

JANUARY 20. (Combined with the Auxiliary.)

MARCH 24.

MAY 12. Annual Meeting. (Harlow Dinner.)

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING

THURSDAY, JULY 9

THURSDAY, JULY 9

*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

5:00 p.m. Case Presentation and Pathological Discussion followed by a Subject of Special Presentation. Joslin Amphitheater, New England Deaconess Hospital.

*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, JULY 10

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.

*12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, JULY 11

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.

*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, JULY 13

*8:00–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.

*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff, Cheever Amphitheater, Dowling Building, Boston City Hospital.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

TUESDAY, JULY 14

9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.

*12:00 m.–1:00 p.m. Pediatric Rounds, Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.

5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.

*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical), Faulkner Hospital.

WEDNESDAY, JULY 15

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.

*12:00 m.–1:00 p.m. Medical Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.

12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheater, New England Deaconess Hospital.

12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.

*2:00–3:00 p.m. Pediatric Conference for Practitioners. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.

*4:00 p.m. Thoracic Conference. Held by Overholt Clinic. Harris Hall, New England Deaconess Hospital.

*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.

*Open to the medical profession.

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